

Wrightman Prize in Clinical Medicine 1921

A CASE OF CONGENITAL HEART DISEASE.



Case I.

A. J. Wilson.

A CASE OF CONGENITAL HEART-DISEASE.

Daniel G. Aet 6 Yrs.

Admitted to Ward 29, R.I.E. on 7th June 1920
under care of Dr Rainy.

Complaint:- Breathlessness. Giddiness. Blueness of the Skin.

Duration:- 3 Years.

History of the Disease.

The following history was obtained from the parents. At birth the colour of the skin was quite normal and the child appeared to be perfectly healthy. In 1917 at the age of 3 years, the above symptoms first made their appearance. His mother noticed a distinct blueness in the lips, ears, fingers and toes and the boy suffered from great breathlessness. In 1918 he began to complain of pain in the chest and was twice in Ward 32 for treatment. He was somewhat improved on discharge but shortly after, his mother began to notice that the tips of the fingers of both hands - and to a less extent those of the toes - were becoming enlarged. Since then the duskiness of the skin has progressively increased, until now it is much worse than even it has been before.

Previous Illnesses:- None. No history of Rheumatic Fever.

Family History:- Both parents are healthy. Two younger brothers both perfectly well.

State on Examination. (25.5.20)

Marked cyanosis and duskiness of the whole body, especially noticeable in the extremities (fingers, nose, ears etc.) and on the mucous membranes. Bulbous enlargement of the soft parts of the terminal phalanges of the fingers and toes with over-curving of the nails both transversely and longitudinally "clubbing". The attitude of the patient is restless. Internal strabismus of the right eye.

Temperature 97.4°.

Weight 2 stone 6 lbs.

CIRCULATORY SYSTEM.

A. Subjective Phenomena:-

Breathlessness is very marked and is sometimes so extreme that the patient is unable to answer questions.

Pain. Occasionally attacks of pain set in gradually and become so distressing that the child seemed stupefied by it and/

and ceased for the time to be conscious of his surroundings. These attacks are associated with exaggeration of the cyanosis.

Palpitation is constantly present, and walking is impossible because of the giddiness. He has to be carried about.

Coughing:- severe attacks come on 3-4 times a day, and during these paroxysms patient becomes extremely cyanotic and looks as though he would choke. The cough is dry - there is no expectoration.

B. Objective Examination.

- (1) The Pulse:- Artery wall thin and elastic. Frequency 112.
Rhythm regular in time and force. Amplitude feeble.
Both pulses are synchronous.

(2) Blood Pressure. (Sphygmomanometer):-

Systolic 100 m.m. Hg.

Diastolic 75 m.m. "

The pulse was too small to get a sphygmographic tracing.

(3) The Heart.

(a) Inspection. Duskininess of skin of thoracic wall, and dilatation of superficial veins. Some bulging of the praecordia, especially over 4-6th left costal cartilages. Diffuse pulsation in 5th and 6th interspaces in left mid-clavicular/

clavicular line. Marked epigastric pulsation. Venous pulsation in root of the neck.

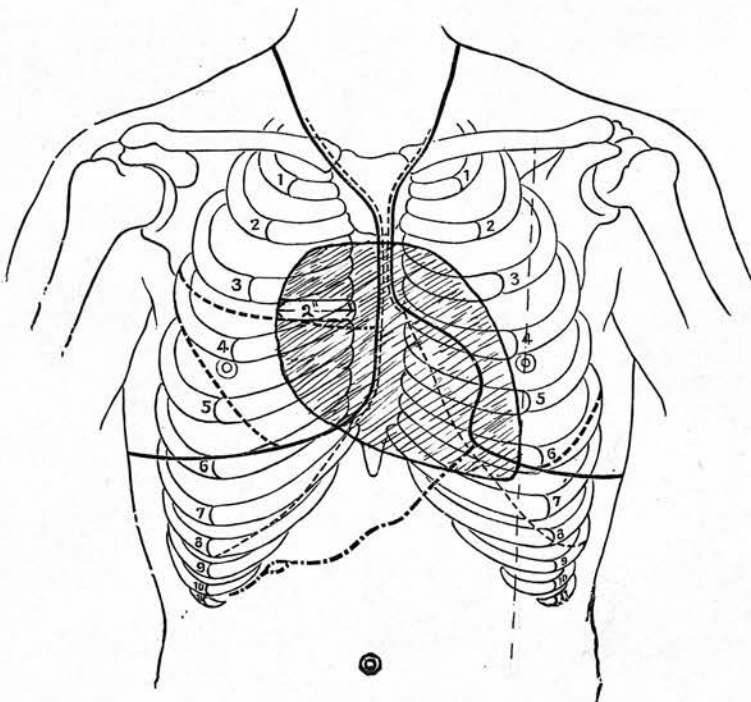
(b) Palpation.

Cardiac impulse feeble. Marked and prolonged thrill, systolic in time, best felt over the 3rd left intercostal space close to the sternum. Apex beat - 6th space in left mid-clavicular line.

(c) Percussion.

Area of cardiac dullness.

$\frac{11}{11}$	
2	$3\frac{1}{2}$



Area of Deep Cardiac Dullness.

The heart is thus markedly enlarged on the right side, and to a less extent on the left.

(d) Auscultation.

Loud rumbling bruit, purely systolic in time, with its maximum intensity in the 2nd left intercostal space and 3rd rib close to the sternum, but also audible over the greater part of the praecordial region, and over both sides of the chest both in front and behind. The direction of propagation was irregular (see diagram) but was propagated least towards the apex where the sounds appeared to be fairly clear. The second sound was fairly distinct in the aortic area but very faint in the pulmonary.

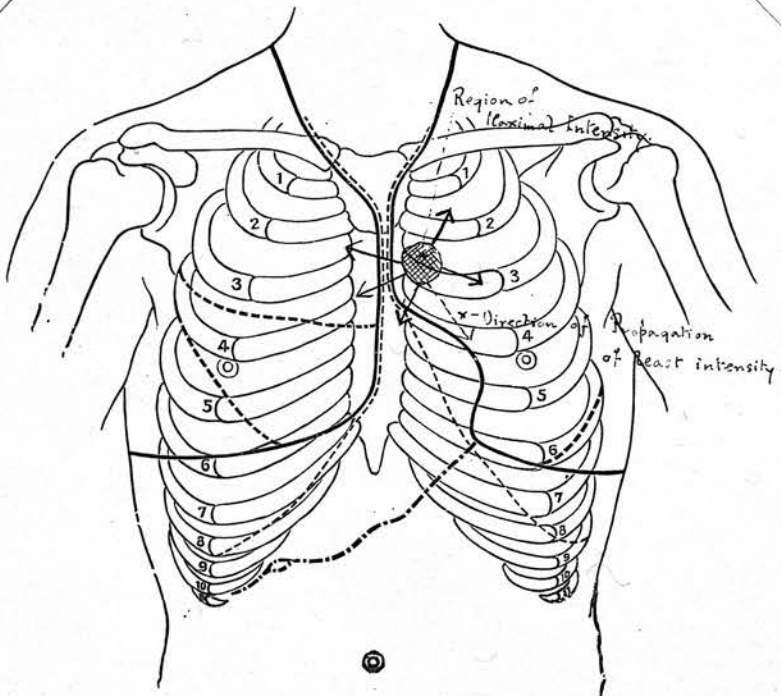


Diagram showing position of maximum intensity
and propagation of bruit.

Electrocardiographic Evidence.

(No. 2396. 14.6.20)

A. Derivation I.

Electrodes arranged to lead the currents from the two arms.

(a) Auricular complex.- P. is well-marked and is notched.

P - R. interval = 0.13 second.

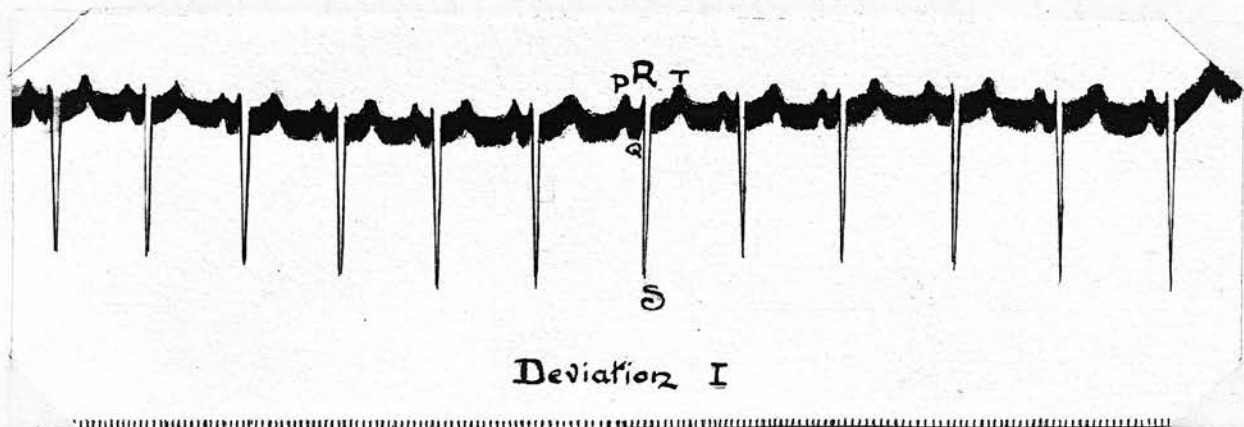
(b) Ventricular complex - quadriphasic.

Q deflection and R deflection - inverted.

S deflection - much exaggerated.

T deflection - exaggerated and notched.

The directions of the chief deflection (S) and the end deflection (T) are opposite.



Duration QRS = .110 second.

Duration of full ventricular complex = 0.332 second.

The duration of group deflections QRS is therefore slightly greater than normal (0.10 second) but bears the normal relationship (1:3) to the full ventricular complex.

B. Derivation III.

(a) Auricular complex - P. wave is slight as compared with lead I.

P - R interval = 0.13 second.

(b) Ventricular complex - quadriphasic.

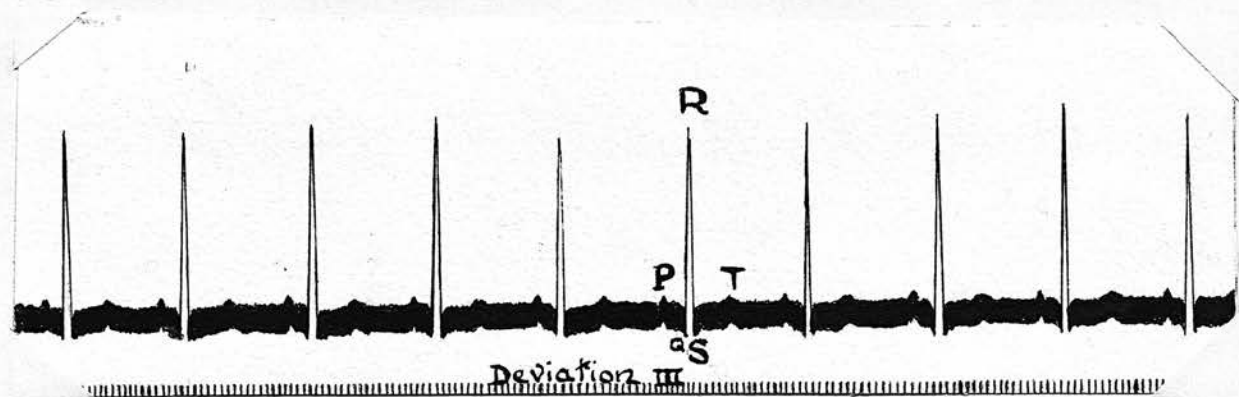
Q deflection - slightly increased.

R " - markedly exaggerated.

S " - slight inversion.

T " - slight diminution and notching.

The directions of the chief deflection (R) and the end deflection (T) are the same.



Duration QRS = 0.105 second.

Duration of full ventricular complex = 0.332 second.

The duration of group deflection QRS is thus slightly greater than normal (0.10 second), and is very slightly below the normal time relationship to the full ventricular complex (1:3).

Interpretation.

Owing largely to the studies of Lewis we now know that the normal ventricular electrocardiogram is in reality a composite picture, depicting the superimposed ventricular activities. In other words, the first portion of the normal electrocardiogram is a composite of 2 curves; it represents the summated effects of right and left ventricles. Because it is a composite curve, consisting of the summated effects of the right and left ventricle, Lewis has termed it the Bicardiogram.

Therefore, the first step in the analysis of the normal electro-cardiogram or bicardiogram, consists in the separate analysis of its two components, i.e. the dextro-cardiogram or the element represented by the activity of the right heart, and the levo-cardiogram - the moiety represented by that of the left side. Now to carry out this analysis, Lewis has introduced a highly technical electro-mathematical technique (the calculation of the "electrical axis"), and his conclusions are as follows.

The human electrocardiogram, taken from whatever lead, is a composite of left and right effects. Its earliest events are those associated with the activation on the septum on the right and left side; the activity of this part is responsible for Q and the commencement of R in all leads. Q and the chief part of the limb R are right-sided events in leads II and III, left-sided in lead I. S. is a right-sided event in lead I, and a left-sided event/

event in leads II and III. Therefore, it is not unreasonable to suppose that, if from any reason whatever, one side of the heart preponderate over the other, its electrocardiographical manifestations will similarly predominate over those of the opposite heart. Thus in left-sided preponderance there would be an exaggerated R in lead I and an exaggerated S in lead III, while the converse picture, namely an exaggeration of S in lead I and of R in lead III (as in the present case), would be found in right-sided preponderance.

By the term preponderance is meant, not enlargement of that side of the heart, but a disturbed balance between the mass of muscle on the right and left sides, i.e. a muscular hypertrophy. Further, the left ventricle may be hypertrophied and the signs of right preponderance appear, if the right ventricle is hypertrophied in greater proportion, just as the signs of one or other preponderance may be seen when the heart as a whole is not enlarged.

These electrocardiographic manifestations of hypertrophy were described by Einthoven as long ago as 1903, and since that time the following evidence has accumulated and "it is now sufficient to establish his signs as the most reliable which we possess of preponderance of one or other ventricle." (Lewis)

- (1) If a series of cases of mitral or pulmonary stenosis be examined electrocardiographically the average curves obtained exhibit Einthoven's signs of right ventricular preponderance.
The/

The weights of the separated ventricles in a similar series shows in the average, preponderance of the right ventricle.

- (2) If a series of cases of aortic disease is examined Einthoven's signs of left ventricular preponderance are found in the average curves, and the weights of the separated ventricles in a similar series shows preponderance of the left ventricle.
- (3) The heart of a child possesses a relatively heavier right ventricle from the time of birth to 3 months after birth. The signs of right preponderance are always present in the child at birth and disappear about the 3rd month of extra-uterine life.
- (4) In instances in which the electrocardiograms have been obtained and in which the weights of the separated ventricles have been taken, the correspondence between the electrocardiographic signs and the ratio of weights of the right and left ventricles has been remarkably exact.

In interpreting such signs of preponderance of one or other side, one fallacy has to be borne in mind. It is this, - that the changes in right and left preponderance are qualitatively identical with the changes discovered when respectively the right and left divisions of the A - V bundle are/

are defective. Briefly there is a close resemblance between the initial phases of the electrocardiogram when there is left preponderance and when the right division is defective; and there is a similar resemblance between these phases when there is right preponderance and when the left division is defective. Thus, if one ventricle (the left) preponderate, then in the dual curves taken from both ventricles, the levocardiogram will preponderate, and inasmuch as the left ventricle is the more massive, in so much will the levocardiogram impress itself on the combined curve. Per contra, when the right ventricle preponderates, then in the dual curves taken from both ventricles, the dextrocardiogram will preponderate. In extreme instances of left or right preponderance, the electrocardiograms in their initial phases resemble levocardiograms and dextrocardiograms (respectively) in the closest details.

Now the initial phases of the levocardiogram as opposed to those of the physiological curves invariably exceed 0.10 second in duration and average 0.14 second, while the duration in the normal heart is never more than 0.10 second, constituting rather less than one-third of the full ventricular complex. This increase is due to defect in the right division of the A - V bundle and to the consequent delay of spread in/

in the right ventricular. A similar, though less pronounced, prolongation is seen in the curve of left hypertrophy, though here it is attributed to delay in the spread of the excitation wave, consequent upon the thickness of the left ventricle.

But the curves of hypertrophy may at once be distinguished from those of defects of the corresponding division of the A - V bundle which they resemble, by comparing the initial phases of the curves.

- (1) The characters of the corresponding monocardioqram are not fully displayed - the amplitude of the deflection is not so great.
- (2) The duration of the initial deflection is not so great. Thus in the monocardioqram the average duration is 0.14 second and always exceeds 0.10 second, while in the present case it is 0.11 second.
- (3) In monocardioqrams the directions of the chief deflection and the end-deflection in all leads are opposite; while in curves of hypertrophy this is not so. In the present case the directions are opposite in lead I, but not in lead III.

It/

It may therefore be definitely concluded that there exists a relative and ^{further, from preceding considerations, an} ~~therefore~~ absolute enlargement (from hypertrophy) of the right heart in the present patient.

The exact interpretation of the notching and exaggeration of P. in lead I, is not very certain; but Mackenzie has found that such a modification in the P. wave, (which is that associated with auricular systole), is frequently associated with a hypertrophy of the auricle. This hypertrophy of the right auricle is suggestive of either some obstruction in the right atrio-ventricular orifice (probably by a stenosis), or hypertrophy from overwork associated with lesions such as a patency of the inter-auricular septum.

As to the significance of the changes in the end-deflection T:- "Alteration in the value or direction of T, both of which are commonly seen in cases of heart disease, have not as yet received any adequate explanation." (Lewis)

Conclusion. The electrocardiogram reveals a preponderating activity (from hypertrophy) of the right side of the heart.

Haemopoietic System.

The blood was darkly venous in appearance. A stained film showed no abnormal cell elements. The red cells were rather small.

Erythrocytes	8,987,200
--------------	-----------

Leucocytes	7,156
------------	-------

Haemoglobin	140%
-------------	------

Colour Index	.78
--------------	-----

The blood thus shows a Polycythaemia.

Respiratory System.

Dyspnoea as noted. Dry cough. A few moist rales over both bases. Otherwise nothing to note.

Nervous System.

Internal strabismus of left eye present since birth. Occasional severe headache. Irritability of temper at times.

Remaining systems - nothing of note.

D I A G N O S I S.

Before discussing this it might be well to summarise briefly the main points of the case.-

I. Cardiac.

- (a) Systolic bruit best heard in the 2nd left space close to the sternum, atypically situated and propagated.
- (b) Increase in cardiac dulness especially on the right side and evidence by electro-cardiograph of hypertrophy of the right heart.
- (c) Well marked systolic thrill.

II. Extra-cardiac.

- (a) Polycythaemia.
- (b) Clubbing of the fingers.
- (c) Cyanosis.

The first question to be settled is, is this a congenital condition which has only gradually manifested itself after some years of post-natal life, or has it been acquired since birth? The following considerations will help to elucidate this.-

- (1) The atypical situation and propagation of the murmur is not that met with in acquired valvular lesions.
- (2) The marked enlargement of the right heart as compared with the left and the feeble apex beat.

Acquired heart disease in children is accompanied by increased force of apex beat, because its effect falls first on the left side, while the dilatation of the right heart sets in later and does not affect the increased strength of the apex-beat. Even the comparatively slight enlargement of the left side present, may be explained by the possible presence of one of the congenital conditions discussed in the differential diagnosis, viz. interventricular communication, for the latter greatly interferes with the circulation, and leads to enlargement and hypertrophy of the left heart.

- (3) "Cyanosis is not met with to any extent in childhood as a post-natal endocarditis; its presence therefore generally indicates a congenital lesion".

(Dr John Thomson).

- (4) The loudness of the murmur taken along with the age of the child is in favour of a congenital condition.
- (5) "The comparative absence of murmurs at the apex while they are distinctly present over the auricle and in the region of the pulmonary orifice, is more in favour of septal defects or pulmonary stenosis than of acquired endocarditis". (Hoehsinger).

Differential Diagnosis.

Systolic bruits occurring in children, most intense in the 2nd left space and 3rd rib close to the sternum (i.e. in the pulmonary area) may be caused by the following conditions.-

- (1) Congenital Heart Disease especially Congenital Pulmonary Stenosis, Patent Ductus Arteriosus, Patent Foramen Ovale or defects in the Interventricular Septum.
- (2) Functional Bruits. These alter with the position of the patient (while those of congenital disease are constant), and often associated with a "bruit de diable" and there is usually no dilatation of the right side of the heart. These may thus not be considered further.
- (3) Acquired Pulmonary Stenosis - this is very rare, and there is usually a history of rheumatic fever.
- (4) Systolic bruits due to other valvular lesions may also be heard over the pulmonary area, but they have their maximum intensity over other parts of the Praecordia. Further evidence has already been adduced against an acquired condition.

One is thus left with the above mentioned congenital lesions.

A. Patent Foramen Ovale.

The bruit is here, contrary to what might be expected, as often systolic in time as pre-systolic or diastolic (Dr John Thomson). It is however usually best heard about the level of the 3rd space or 4th rib, and clubbing of the fingers is not so common here as in other conditions, as the patency of the communication prevents systemic venous congestion.

B. Patent Ductus Arteriosus.

Here the murmur is not purely systolic but continues through both systole and diastole, with its maximum intensity at the time of the 2nd sound, and it is best heard in the 3rd left space about $\frac{1}{2}$ " out from the sternum. Further the condition seldom presents cyanosis, clubbed fingers or polycythaemia.

C. Patent Interventricular Septum.

The murmur here is most intense lower down the sternum - usually the two 3rd spaces, and the systolic thrill is absent.

D. Pulmonary Stenosis.

The bruit here is purely systolic, maximal in the 2nd left space close to the sternum, but also audible over the greater part of the praecordia. It is accompanied by a systolic thrill, cyanosis, clubbing of the fingers, and polycythaemia./

polycythaemia. Further, it is the commonest congenital condition met with in practice - "80% of children with congenital heart disease who reach 12 years suffer from this lesion" (Peacock).

"Lastly, the abnormal weakness of the pulmonary second sound along with a distinct systolic murmur can only be explained in early childhood by assuming the presence of a congenital pulmonary stenosis" (Dr John Thomson).

But from a strict diagnostic point of view one cannot say that the three preceeding lesions may not one or all be present too, for "pulmonary stenosis is usually accompanied by patency of the interventricular or inter-auricular openings or both, and often also by an open ductus arteriosus" (Dr John Thomson).

One thus gets not a pure clinical picture but a syndrome and the presence or absence of any one of the above conditions cannot with certainty be stated, until death.

Prognosis.

Few marked cases of congenital heart disease survive to adult life. The prognosis must depend upon the evidences of cardiac efficiency, upon the strength and age of the patient, and upon the presence or absence of cardiac hypertrophy and cyanosis, rather than upon any opinions as to the nature of the malformation. The character of the murmur is of little import./

import. The marked cyanosis and dyspnoea, and breathlessness on exertion, and the cardiac enlargement in the present case are therefore of grave significance.

In both patent foramen ovale and deficient ventricular septum there is the risk of sudden death from cerebral embolism in thrombus formation, while in the latter the communication with the left ventricle causes greater interference with the circulation and leads to early cardiac hypertrophy.

Treatment.

Generally the only possible treatment is to keep the patient warm and protect him from chills and especially bronchitis, to protect him from undue excitement and emotion, and to prevent any embarrassment of the heart from flatulence by careful dieting. For periodic signs of cardiac failure (e.g. increasing dyspnoea), digitalin and strophanthin give good results, but these cardiac tonics have no effect on the habitual cyanosis of these cases. The question of the treatment of the cyanosis by oxygen will be referred to later.

Progress Notes.

The condition remained more or less stationary, though the dyspnoea under treatment became less marked; the patient was transferred to the Edinburgh Hospital for Incurables on 9.9.20.

C O M M E N T A R Y.

Etiology of Congenital Heart Disease.

This in many cases is largely hypothetical.

- (1) In some cases the abnormalities in the heart are apparently of such a nature that they must have resulted from intra-uterine endocarditis though some authorities consider this is rare.
- (2) In many cases part, or whole, of the lesion consists in the persistence of openings in the septa. Abnormal patency of these is usually referred to obstruction to the course of the circulation occurring at a period earlier than that of their normal closure. In the present case the obstructing factor is presumably the stenosis of the pulmonary orifice. The pressure on the right side of the heart would then be too great to allow of closure of the septum between the two sides so that it remains patent in either its auricular or its ventricular portions (or both). The deficiency in the exit of blood from the right ventricle will be made good to some extent by the ductus arteriosus remaining open. Hence the explanation of/

of the fact that "pulmonary stenosis is usually accompanied by patency of the interventricular or inter-auricular openings or both, and often also by an open ductus arteriosus".

(Dr John Thomson).

- (3) Defects due to imperfection of development. Ballantyne suggests that the same morbid influences which occasion endocarditis in the later stages of intra-uterine life, give rise to developmental defects when they act in the earlier months, i.e. that the morbid influence which in the young embryo produces a teratological effect, has a pathological effect when it acts on a foetus which has so far developed as to have differentiated organs.

The two outstanding clinical features of congenital heart disease, viz. the Cyanosis and the Polycythaemia, call for some comment.

Cyanosis is present in the majority of cases of congenital heart disease and it is so characteristic of these cases that the condition has been called "morbus caeruleus" - the dark-blue disease. It differs from cyanosis from other causes in degree rather than in kind. As already noted, cyanosis is not met with to any extent in childhood as a post-natal endocarditis; its presence therefore generally indicates a congenital heart condition.

The/

The causation of the extreme cyanosis has been the subject of much discussion. Among others, the following theories have been brought forward from time to time.

- (1) That it is due simply to admixture of the venous and arterial blood allowed by the defective separation in the abnormal heart. This view is open to question as Young records a case (Journal of Anatomy & Physiology 1907, vol. XLI, p.190) in which there existed only a trace of an interventricular septum and yet there was no cyanosis until the heart began to fail.
- (2) That it is merely the result of congestion of the venous system arising from backward pressure, especially when the blood is abnormally dark from its concentration. In some cases however with marked cyanosis signs of backward pressure may be entirely absent.
- (3) That the cyanosis is simply an indication of the extent to which the circulation of the blood in the lungs is being hindered, the discoloration being due, not to venous congestion pure and simple, but to congestion with non-aerated blood. This is borne out by the results of Morrison's analysis of 75 cases (Practitioner. Vol.XL, p.101, 179) which show that "obstruction in the pulmonary artery is the lesion most commonly associated with cyanosis". If sufficient blood cannot enter the lungs, cyanosis is/

is inevitable. That such blood as does go to the lungs is adequately oxygenated is shown by failure of oxygen inhalations to benefit the cyanosis. The conclusion, therefore, seems to be that so long as there is free admission of blood to the lungs, cyanosis does not occur, even though the streams mix.

The Polycythaemia.

The only way in which the body can compensate for this obstruction in the pulmonary artery is by charging the blood more highly with corpuscles so that the oxygen capacity of that portion which does reach the lungs will be increased. The smaller size of the corpuscles is a further means of increasing the amount of surface of haemoglobin so that it can the more readily take up oxygen.

A CASE OF DIABETES INSIPIDUS.

Case II.

A. J. Wilson.

A CASE OF DIABETES INSIPIDUS.

Mrs Isabella C. Aet 29. Housewife.

Admitted to Ward 33 on 31.10.19 under care of
Prof. Sir Robert Phillip.

Patient's Complaint:- Increased frequency of micturition
and extreme thirst.

Duration - 4 years.

History of the Present Disease.

Four years ago patient noticed that she was passing water more frequently than normal and she began to experience unusual thirst. Patient cannot remember any fright or emotional experience prior to the onset of this condition. These symptoms developed gradually and during the past 4 years they have become progressively worse. Latterly patient has begun to feel exhausted and easily tired.

Previous Illnesses.

Patient contracted Syphilis from her husband about 8 years ago, and has received no treatment for this. Scarlatina, measles/

measles and whooping-cough in childhood. Otherwise the health has been quite good.

There is no history to be obtained of any injury to the skull at any time.

Family History.

One sister aet 16 died of "fits" - Epilepsy (?).

Beyond this, nothing to note in the family health.

The home surroundings appear to be fairly satisfactory.

State on examination (1.11.20).

The patient is well nourished and healthy looking. The colour is good. Weight 10 stone $2\frac{1}{2}$ lbs. Temperature subnormal - 97.2° .

URINARY SYSTEM.

A. Subjective Phenomena.

The increased frequency of micturition (once every hour during the day and every two hours during the night) causes great distress and prevents proper sleep. For the progress of the amount passed per diem see chart. Thirst is excessive and the amount of water taken is indicated graphically on the chart. There is no pain or uneasiness in micturition nor is there any pruritus over the vulva.

B. The Urine.

The quantity varies from day to day (see graph). On the day of examination it was 140 ozs.- roughly 4 litres. It is very pale in colour with a yellowish-green tinge, and has no odour.

Reaction - Acid. Specific Gravity low - 1004.

No albumen, blood, bile, sugar, acetone or di-acetic acid present.

Total solids = 9.32 grams per litre, giving a daily output of solids of 37.28 grams, as compared with the normal 60-70 grms per diem. The percentage of solids is thus diminished, and to a much larger extent than the total amount of them excreted per diem since the amount of urine is very much larger.

Chlorides = 18.2 grms. per diem. The average in health per diem being 12 grm., they are here absolutely increased but relatively diminished.

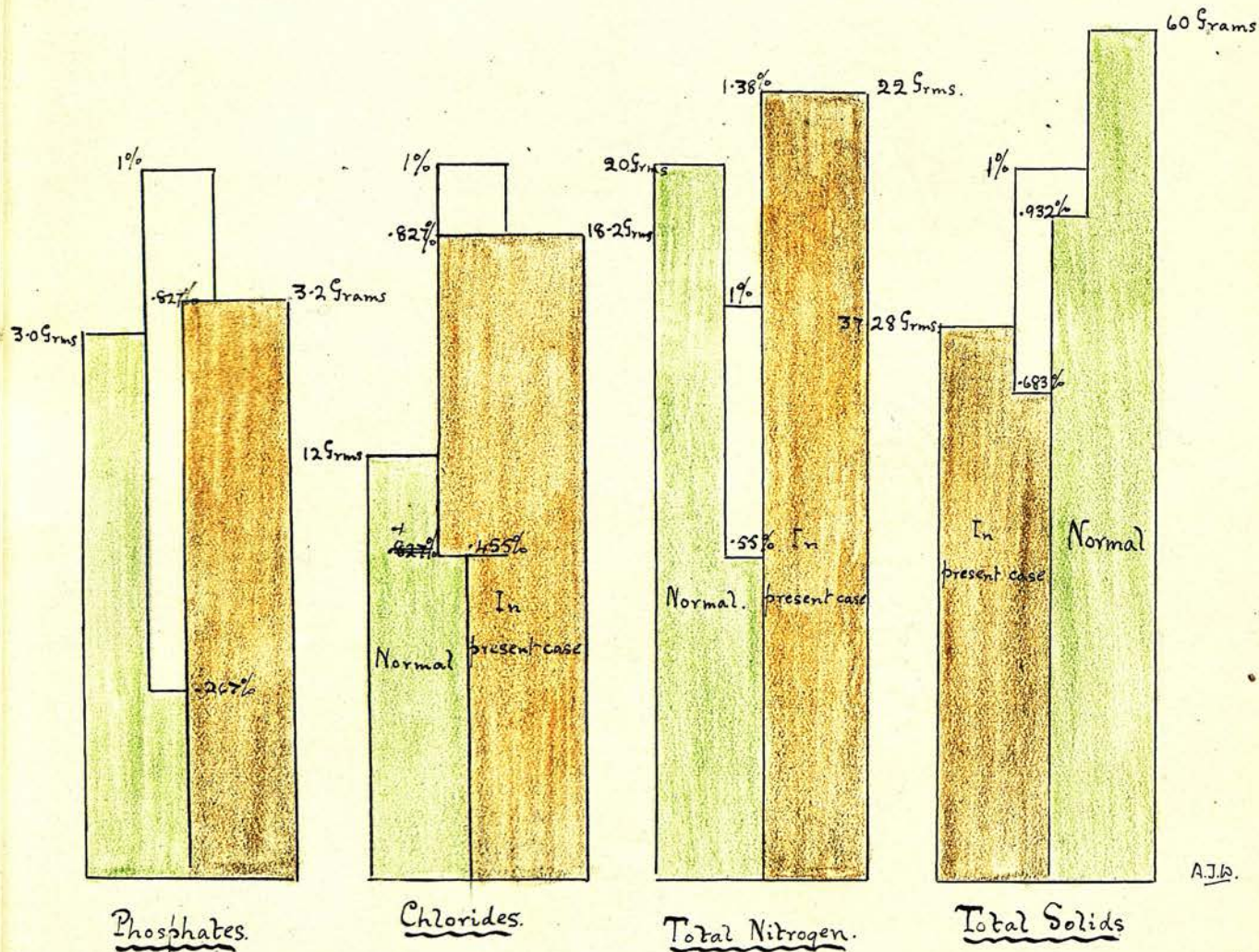
Phosphates (as phosphoric anhydride) = 3.2 grms per diem.

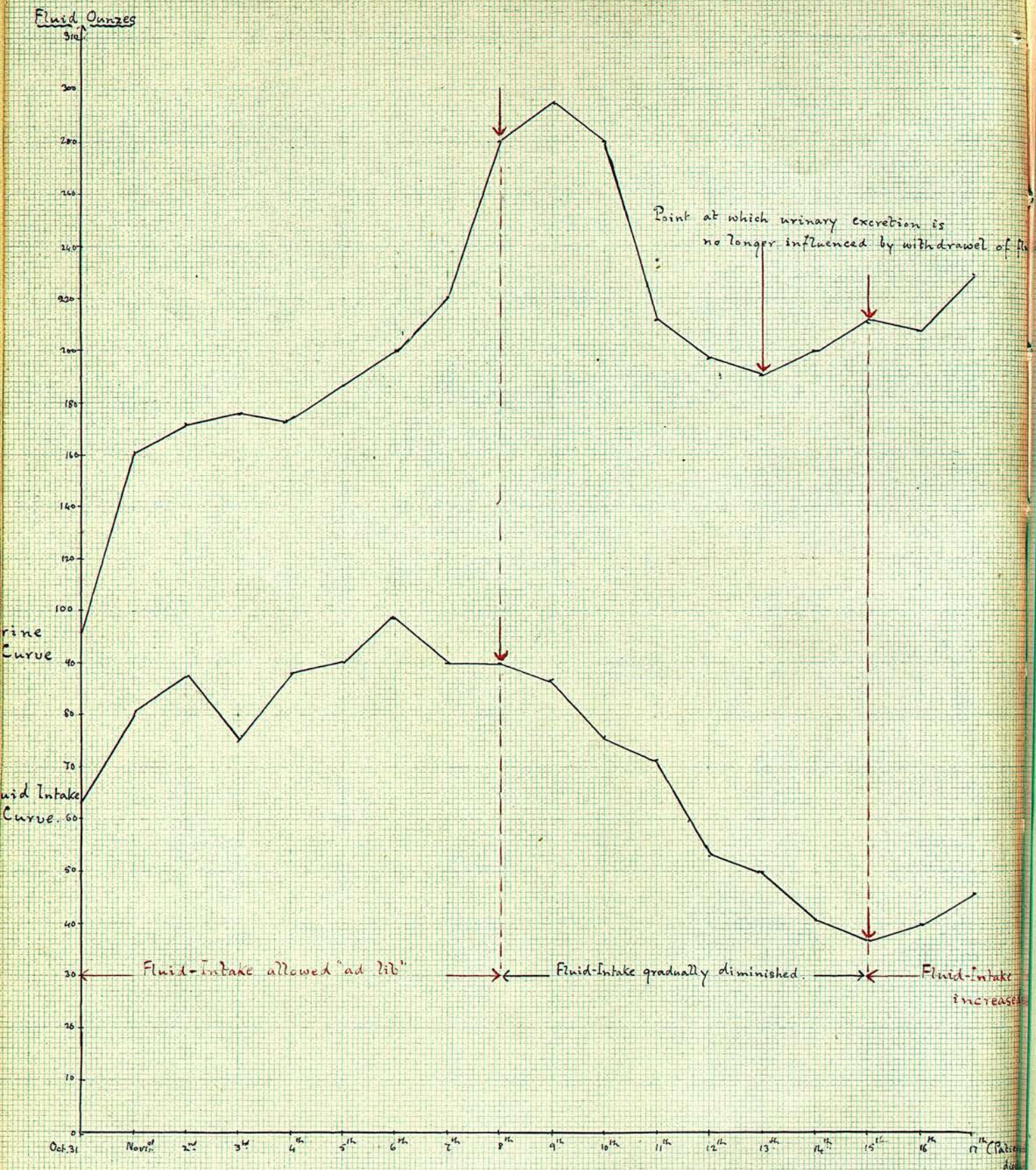
The average daily excretion in health being 2-3 grms., these are absolutely slightly increased but relatively diminished.

Total Nitrogen per diem (Kjeldahl's method) = 22 grms as compared with 15-20 grms. per diem in health.

The quantitative changes may thus be summarised:-
The percentage of total solids is small, the chlorides and phosphates are increased, and the Total Nitrogen is slightly increased.

On centrifuging, the deposit contained some epithelial cells and a few crystals of oxalate of lime.





Graph to illustrate ratio of Urinary Excretion to Fluid Intake.

The chart illustrates the fact that the amount of urinary excretion exceeds considerably the amount of fluid ingested, the surplus being made up from the food and the tissues of the body; and that restriction in fluid intake diminishes the urinary excretion up to a certain point only. (The disproportion is lost, however, at a later stage when the tissues have become dehydrated. (Prof. Boyd)).

Alimentary System.

Appetite good but not voracious. Digestion unaffected. Marked tendency to constipation. No other subjective phenomena.

Haemopoietic System.

Red Cells	4,527,000
Haemoglobin	90%
Leucocytes	7,125
Colour Index	1.

Wassermann Reaction +++.

Circulatory System.

No subjective phenomena.

Pulse 72, regular in time and force. Artery wall soft.

Heart/

Heart	$\frac{III}{1/3\frac{1}{2}}$	Blood Pressure	(Systolic 120 m.m. Hg.
		(Syphymograph)	(Diastolic 85 " "

Sounds closed in all areas except in aortic where the 2nd sound appears to fade off into a soft blowing bruit.

Integumentary System.

Skin dry and harsh. Tingling and itching of skin occasionally. Boil on left forearm.

Reproductive System.

1 child aged 5 alive and healthy. One miscarriage.

Nervous System.

Patient suffers at times from pain in the back and legs and headaches, often intense, over both temples.

Eyesight is poor.

Visual Acuity	(Right Eye	$\frac{6}{20}$
	(
	(
	(Left "	$\frac{6}{35}$

By Ophthalmoscopy nothing abnormal seen in the fundus.

No alteration in the fields of vision. All reflexes are normal. Nothing further to note.

Differential/

Differential Diagnosis.

Before considering this it is essential in every case of Diabetes Insipidus to examine the blood by the Wassermann Reaction for the presence or absence of active syphilitic infection, which as noted is existent in the present case.

The low specific gravity and the absence of sugar in the urine exclude Diabetes Mellitis. Four other conditions must be considered. -

(1) Hysterical Polyuria. This is always transient and is accompanied by other hysterical manifestations.

(2) Chronic Interstitial Nephritis. Here albumen and hyaline casts are usually present and there are marked changes in the circulatory system - high blood pressure, thick arteries, and a hypertrophied left ventricle.

(3) Intermittent Hydronephrosis is transient and cyclical.

(4) The persistent polyuria with marked thirst and absence of sugar and albumen justify the diagnosis of Diabetes Insipidus.

Prognosis.

Prognosis in Diabetes Insipidus is difficult. It depends entirely on the etiological and pathological factor in the particular case under consideration, and this, as will be pointed out later is not easy to elucidate. "Idiopathic" cases may last/

last for years and terminate in a gradual loss of nutrition and an intercurrent attack of Pneumonia or a slowly progressing Tuberculosis. With a gross cerebral lesion prognosis is bad.

Progress Notes.

Under the treatment prescribed below patient's urine gradually diminished to a certain point, below which it could not be reduced (see chart). She was accordingly discharged on 16.11.20, feeling considerably better.

Treatment.

This is not entirely satisfactory. The primary essential in every case, is, as Prof. Boyd has insisted, to discover if possible, whether a definite dyscrasia, such as syphilis or tuberculosis exists as a causal factor, and if so to direct treatment primarily to its amelioration by suitable remedies. So in the present case, treatment by Novarsenobillon ^(weekly) .45 gram, was commenced from the start.

Apart from this, drug treatment has, for the most part been directed to influencing the condition through the nervous system. Valerian, ergot, nitro-glycerine, antipyrin, and various salts have been used with more or less success, but though they may in fact diminish temporarily the excessive polyuria and improve the general health, they do not cure the/

the disease. The hypodermic injection of extract of posterior lobe of Pituitary in treatment- to the action of which reference will be made later - causes disappearance of the polyuria for about 12 hours, and by repeated injections the patient can thus be given a respite, particularly at night, from the constant disturbance involved by the polyuria. Electricity applied to the medulla has had a marvellous curative effect in some cases.

As regards diet, fluids were not unnecessarily restricted, as such restriction has a deteriorating effect on the general health. A gradual diminution in fluid intake was carried out until the urinary excretion was no longer influenced. (see chart illustrating this point in the present case). Thirst was alleviated with ice, acidulated water and small doses of pilocarpine, the diuretic caffeine beverages being avoided. Nutritious and easily digested food, containing the minimum of salt was given in small quantities at frequent intervals. There is no objection to carbohydrate or protein within the limit of the patient's digestion.

General hygiene is of importance - gentle exercise, a bracing climate and as the temperature is subnormal, warm clothing are all important. The trophic condition of the skin was looked after by massage, baths and gentle friction. Constipation was treated by enemata, massage and mild cathartics, drastic purgation being avoided from the liability to set up severe diarrhoea.

C O M M E N T A R Y .
-----Etiology of Diabetes Insipidus.

The disease is a comparatively rare condition. During a period of 6 years, 20 cases were under treatment in the Edinburgh Royal Infirmary. The present case illustrates the fact that the disease is commoner in early life, but is atypical in that the disease is much commoner in males. The predominance of men in the statistics is thought by Schalmann and Desoutter (Rev. de Med. Paris 1920) to be due to the influence of Syphilis, which, as will be seen later, is the outstanding factor in the pathology. The positive Wassermann in the present patient has already been noted. Family predisposition may exist, the disease running through neuropathic families or alternating with other nervous or mental conditions. The death of the sister of the present patient from what appears to have been epileptic fits, is of importance in this connection.

In brain diseases, syphilis in adults plays an important part, and Tuberculosis in diabetes insipidus in children, and it is for this reason that Prof. Boyd so strongly emphasises the treatment of these associated dyscrasias. Chronic hydrocephalus has been present in some cases, and in these cases lumbar puncture is often beneficial. (Maranon. Journ. Amer. Med./

Med. Assoc. 1919).

Pathology of Diabetes Insipidus.

The association of the condition with pituitary disease and disturbance has long been recognised. Kennaway and Mottram (Quat. Journ. of Med. 1919) state that "there do not appear to be any cases on record in which diabetes insipidus occurred and in which the pituitary proved post-mortem to be normal, or where it was normal, the stalk free from pressure".

Schaefer has shown that the injection of extract of the posterior (infundibular) lobe and pars intermedia, the cells of which are concerned with the excretion of water, has in the healthy animal a profound effect on kidney function, causing vaso-dilatation in the kidney with subsequent diuresis.

In his surgical experience, Harvey Cushing (Boston Med. Journ. 1913) has found polyuria and polydipsia frequently following on injuries involving the base of the brain and in many cases haemorrhage into the pituitary body was found.

Pathologically, the disease, par excellence, of the pituitary and neighbourhood is Syphilis; while from the medical side Prof. Boyd has shown that analysis of many cases of Diabetes Insipidus, reveals in a large percentage of cases, lesions involving the base of the brain especially a gummatous process/

process in the pituitary itself or a gummatous meningitis affecting the middle cranial fossa. Further, the polyuria which is such a frequent symptom in hypopituitarism - in both acromegaly and dystrophia adiposis genitalis - is well known.

In some cases, further evidence of pressure on the gland is present in the form of primary optic atrophy, often with bitemporal hemianopsia, the frequent association of which with the encephalic polyurias classified as Diabetes Insipidus, was commented on by Fitcher years ago. Cushing suggests that even the present so-called "idiopathic" cases of diabetes insipidus will be found on examination to be sympathetic manifestations of pathological changes involving the hypophyseal neighbourhood and that even the "emotional" (hysterical) polyurias are in all likelihood a urogenic discharge of pituitary secretion.

The usually accepted pituitary origin of diabetes insipidus has been disputed by Houssay and Camus and Roussay very recently on the grounds that they have produced it by puncture of the base of the brain near the corpora mammillaria and that pituitary extract has not any specific action apart from the fall of blood pressure and vomiting induced by its sudden introduction in the veins.

Their/

Their position appears to be somewhat strengthened by certain clinical observations, for it is found that after injections of pituitary extract the polyuria of diabetes insipidus of hypophyseal origin disappears after about 12 hrs. The effect is very rapid (but, unfortunately rather transient) so that an hour after the administration of 1 cc. of the extract of the posterior lobe it is impossible to distinguish the urine of a patient with diabetes insipidus from that of a normal person.

Now here we have what appears to be paradoxical. For the physiological effect of extract of posterior lobe is, in the normal animal, polyuria. Further, as pointed out by Harvey Cushing as long ago as 1911, it is difficult to harmonise the diuresis which may accompany hypopituitarism with the a priori expectation that individuals with this glandular insufficiency would show a lower urinary output.

Drs. Kennaway and Mottram, however, in their paper referred to, reply by bringing forward evidence to show that pituitary extract can produce both anti-diuretic and diuretic effects from the presence of two substances, and suggest that the effects produced in any given case will depend on the quantity ratio of these two to one another, the anti-diuretic being in greater proportion or concentration in the pituitary disturbance associated/

associated with diabetes insipidus than in the normal state when the diuretic predominates. They further show that the anti-diuretic effect of pituitary extract in the treatment of diabetes insipidus is due to direct action on the kidney and not on diminished absorption of water from the intestine.

Schulmann and Desoutter (Rev. de Med. Paris 1920) divide cases of diabetes insipidus into 2 groups.-

- (1) Secondary or Sympathetic group, in which the polyuria is secondary to lesions of, or disturbances affecting, the pituitary gland, (especially syphilitic affections), the renal permeability being normal, except for water in regard to which it is exaggerated.
- (2) Primary or Idiopathic groups, in which no organic disease or functional disturbance is present, the origin being probably renal and consisting in an inability to secrete concentrated urine, i.e. the renal epithelium is abnormal. In this group, the administration of NaCl increases the volume, but not the specific gravity of the urine.

In the present patient it is not easy to elucidate the exact nature of the case but all the evidence points to it being a Secondary and Syphilitic Diabetes Insipidus resulting from gummatous disease of the pituitary body or region.

- (1) The positive Wassermann.
- (2) The commencing eye symptoms, which although not yet very definite, are suspicious.
- (3) The bitemporal headache, which according to Harvey Cushing is a constant symptom in pituitary affections. A skiagram of the skull might throw some light on this question.

A CASE OF CARCINOMA PYLORI.

Case III.

A. J. Wilson.

A CASE OF CARCINOMA PYLORI.

James B. Aet 57. Warehouseman.

Admitted to Ward 32 on 2.11.19 under care of
Prof. Sir Robert Phillip.

Patient's complaint:- Pain in the stomach and vomiting
after food.

Duration:- 2 months.

History of the present illness.

About 2 months ago patient first noticed foul gas passing up from his stomach. This was accompanied by a feeling of wishing to vomit. Shortly after this he began to experience a dull discomfort in his abdomen after a meal, which soon developed into sharp pain in the pit of the stomach. This pain was accompanied by nausea and vomiting, sometimes of white material, sometimes of yellow, sometimes of dark brown like chocolate. His appetite began to diminish and his friends noticed that he was getting thinner. His bowels, which had always been rather costive, now became markedly constipated, and 6 weeks from the onset of his illness the faeces became dark-black and tarry in appearance. These symptoms have now become progressively worse.

Previous Illnesses.

Scarlatina, measles, whooping-cough, and small pox in infancy. Erysipelas twice, about 1876 and 1889.

Patient has suffered from "indigestion" since about 1884. The history of this is as follows:- When he was in his early twenties he began to suffer from "indigestion" with a dull gnawing pain in the epigastrium shortly after food, which was eased by taking fluid, especially soda-water. This "indigestion" used to come on in attacks, each of which used to last about 3 - 4 weeks, and would then go away for some 6 - 7 weeks during which patient felt quite well and could eat anything without pain or discomfort. He never had any vomiting or haematemesis during the attacks and he does not remember having seen any alteration in the colour of the stools. Gradually the attacks came more and more frequent and the intervals of good health between, shorter and shorter, until when he was about 26 he was always troubled with indigestion and he has remained a chronic dyspeptic all his life.

(The above history is obviously a typical picture of chronic gastric or duodenal ulcer).

Family History.

One sister aet 30 died of "tumour of the stomach".

Beyond this, nothing to note.

State on Examination (5.11.19)

Patient is a very thin and emaciated, poorly developed man, with marked anaemia and a somewhat cachetic^c look. His intelligence is above the average and he describes his symptoms very graphically.

Height 5 ft. $2\frac{1}{2}$ ins.

Weight 6 st. 13 lbs.

Temperature subnormal.

Alimentary System.

Subjective Phenomena:- The appetite is poor and patient has especially a distaste for meat. He has lost weight rapidly within the last 2 months.

He complains of a dull aching pain in the epigastric region, which is not very severe but is more or less constant. Some days the pain is worse than others and alters with his posture - it is least felt when lying on the left side or back and is worst when lying on the right side, so that patient cannot sleep when lying on that side. It is much increased by the taking of food, especially solid food, and then it becomes severe and colicky in character, shooting round to the back. The pain reaches its maximum intensity about $2\frac{1}{2}$ hours after food and is attended with increasing nausea and then vomiting usually takes place. The vomiting eases the pain very considerably and patient for this/

this reason often used to induce vomiting, if it did not soon take place, by pushing his fingers into the back of his pharynx. The vomited material has a very foul smell and an acid taste. It is composed, sometimes of whitish-yellow matter often with pieces of the preceeding meal in it, and sometimes it is dark-brown or chocolate coloured. Patient states that he has occasionally noticed remnants of a meal of the preceeding day, e.g. raisins, currants, etc.

Sometimes when patient is lying down very foul smelling dark fluid wells up into his mouth without any movements of vomiting taking place.

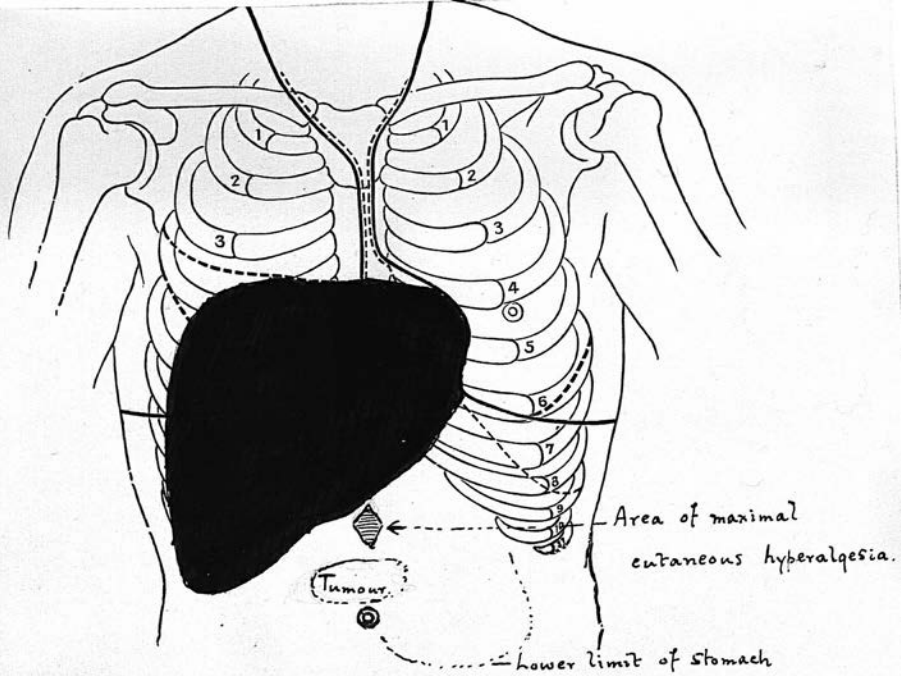
Nausea is always very marked and patient complains constantly of foul eructations and flatulence.

The bowels are very constipated and the motions are dark and tarry in appearance.

Examination of the Abdomen.

On inspection, the skin of the abdominal wall is loose and can be lifted up in big folds - there is little subcutaneous fat. There is no ascites. The abdominal wall looks hollowed out and the costal margin stands up prominently. There is a prominence in the epigastric and umbilical regions especially to the right of the mid-line. Respiratory movements are equal all over.

On/



On palpation, splashing was elicited 6 hrs. after food. In the epigastrium about 2 c.m. above the umbilicus there is felt a distinctly hard, rounded, swelling, surface smooth, contour irregular, lying transversely but extending more to the right than to the left of the mid-line. It moves with respiration and slips away from the palpating finger with a sudden jerk. Pain is experienced over it on pressure, and the recti (especially the right) are resistant over it.

Around the umbilicus itself, 3 or 4 small round hard knob-like bodies can be felt, and an indurated thickened band can be felt extending upwards and to the right towards the liver - apparently the hepatic ligament.

On percussion, the stomach was found to be greatly enlarged and in the recumbent posture descended to the level of the umbilicus.

Hepatic dulness:- The lower margin extended to about $\frac{1}{2}$ " below the costal margin (see chart). Its surface was quite smooth. The upper limit of dulness was over the 4th rib.

Nothing abnormal was found on rectal examination and there was no enlargement of the left supra-clavicular glands.

On examination of the skin of the abdominal wall an area of cutaneous hyperalgesia was found, with its maximal intensity about midway between the umbilicus and the ziphoid cartilage.

Radio-graphic/

Radio-graphic Investigation.

Opaque meal. 1st meal - trace of gastric stasis with the remainder in the proximal part of the caecum with traces beyond. 2nd meal - showed a low J shaped stomach with ill-defined pylorus, in fact no cap was visible and no peristalsis, although the tone of the stomach was fair, it kept the meal suspended for quite a long time, gradually relaxing. Under continued observation, no irregularity of the greater curvature was visible.

2nd day:- want of definition of the gastric region but still a trace of gastric stasis - not seen in the plate because of movement; the large bowel was unevenly filled.

3rd day:- distal colon well and evenly filled.

The X-rays therefore only show a certain irregularity in the limit of the stomach shadow towards the pylorus, a certain obliteration of the pyloric area and delay in the passage of the food. These findings, together with the existence of a large dilated stomach suggests a pyloric obstruction.

Test Meal.

The fluid drawn off was brownish in colour, with froth on the top, with a yeasty, sour, acrid odour.

Chemical/

Chemical Composition:-

Free HCl (Gunzberg's test) - absent.

Lactic, butyric and acetic acid - all present.

Mucin also present.

Total acidity = .066 grams HCl.

The Vomit. (17.11.19)

Sour smelling with dark-brown froth on the surface.

No free HCl.

Microscopic examination:- undigested muscle fibres, starch granules, *tetrad* and *sarcinae* and numerous epithelial cells.

No tumour cells. A film stained by gentian-violet showed some long bacilli (Oppler-Boas?).

Spectroscopic examination revealed the presence of blood pigment derivatives.

The Stools.

Scanty, hard. Black and tarry in colour.

Benzidin test for occult blood - positive.

Haemopoietic System.

Erythrocytes	3,630,000
Leucocytes	7,600
Haemoglobin	58%
Colour Index	.8

Urinary System.

Quantitative estimation of chlorides was carried out (for a purpose to be explained later) and was found to be 11.5 grams per diem, i.e. not much below the normal diurnal excretion. Urine showed nothing abnormal.

Remaining Systems.- nothing to note.

Diagnosis.

This is unfortunately only too apparent. The slow, insidious onset, with vague, gastric symptoms, quickly followed by pain in the epigastrium and vomiting, with constipation and melaena, and clinical evidence of pyloric obstruction and ulceration and metastatic growth, following on a long history of chronic dyspepsia in a man past middle life, forms as typical a picture of advanced inoperable carcinoma ventriculi as one could live to see.

^{ress}Prognosis.

12.11.19. Weight lost since admission - $\frac{1}{2}$ lb. Occult blood in faeces every day except 8, 9, 11, 19. Nausea still present but foul flatulence now disappeared with the dieting and gastric lavage.

17.11.19./

- 17.11.19. Vomited dark foul smelling material with brown froth.
Blood positive. Pain severe - terpene hyd. gr. $\frac{1}{2}$
t.i.d.
- 26.11.19. Mr Alexander Miles examined patient but did not
consider case suitable for operation. Pain severe.
Codeine $\frac{1}{8}$ gr. t.i.d.
- 9.12.19. Patient discharged. Weight increased from 6 st. 13 lbs.
on admission, to 7 st. 2 lbs. to-day.
Occult blood in faeces remained present throughout.

Prognosis.

The prognosis is hopeless. In all probability death will occur from increasing cachexia and exhaustion, terminating possibly in a fatal pulmonary complication.

Treatment.

The indications were to relieve pains, to counteract the vomiting, foul eructations and flatulence by suitable dieting, to treat the constipation, and to improve the general health.

For the pain - $\frac{1}{12}$ gr. heroin hypodermically as required.

Diet - milk diet, soup, chicken, cream.

For the flatulence - aqua menth. pip. $\frac{3}{4}$ s.s. t.i.d.

" " constipation - hydr. c. cret. gr. $\frac{1}{2}$ every night
and daily enemata.

C O M M E N T A R Y. -----

The interest of this case lies in the previous existence of a very definite gastric ulcer in early adult life being followed later by the development of a malignant gastric growth.

The frequency with which this sequela occurs is a point which has been debated almost ad nauseam, and even yet opinion is still divided on the question.

From the clinical side we have the following figures given by various authorities as the percentage of cases of cancer which develop from ulcer. Robson 59%, Rodman 50%, Payr 26%, Kuttner 43%, while Mayo and Moynihan put it as high as 75% and 66% respectively. The latter states (B.M.J. 1920) that in his experience, "in more than half the cases of cancer of the stomach there is a history suggestive of the previous existence of a gastric ulcer".

Pathologically, the evidence points to much the same conclusion. Wilson and McCarty (Amer. Journ. Med. Sc. 1909) found in 71% of cases of gastric carcinoma "sufficient pathological evidence to warrant a diagnosis of preceeding ulcer". Charles Mayo (Annals of Surgery, May 1921) writes, "investigations for many years at the (Mayo) Clinic have led us/

us to reiterate the assertion that gastric ulcer is potentially malignant, although by post-mortem examination of extensive disease causing death it may be impossible to determine that any early ulcer was present. Many ulcers that we believed to be benign, ^{on} excision showed the presence of carcinoma in a limited area of the margin. We, therefore, believe that cancer often develops on ulcer and hyposensitive stomachs obscure the early symptoms". For this reason Mayo goes so far as to recommend routine excision or destruction by cautery of every gastric ulcer which comes to operation.

Moynihan is in complete agreement:- "In about 20-30% of the cases of carcinoma of the stomach removed by operation, the claim that the malignancy present is imposed upon a simple ulcer appears on pathological grounds to be irrefutable." He further says that not less than 10% of cases of gastric ulcer removed at operation show the early stages of cancer. Sherran (1921) found in 14 of 57 specimens of carcinoma of the stomach removed at operation there was definite microscopic evidence that the malignant disease started in a simple ulcer. Among 135 ulcers he excised on a diagnosis of simple ulcer, carcinoma was discovered starting on the edge of the ulcer in 6. Anchutz and Knojectzny (Deut. Zeits. f. Chir. 1920) studied this question both clinically and pathologically and conclude that 3-5% of chronic ulcers later become carcinomatous.

The/

The bulk of evidence therefore appears to be that there is a definite relationship between carcinoma of the stomach and previous chronic ulcer, and the present case is a point in illustration.

Apropos of the difficulty of determining clinically (until microscopic investigation has been carried out) the nature of tumour growths following upon chronic ulcer, the following case (No.A.958) which the present writer recently had an opportunity of studying in Sir Harold Stiles' Clinic, is instructive. A patient of 73 with a typical history of previous gastric ulcer indigestion complained of pain after food and progressive loss of weight but no vomiting. Clinically a large but ^{freely} ~~freely~~ movable tumour was felt in the epigastrium, and a dilated stomach with pyloric stenosis was found radiographically. At the operation a freely movable hard mass was found stenosing the pylorus and extending onto the lesser curvature. The serous coat over it was quite intact, no indurated glands could be discovered, no secondary nodules in the liver, and no metastases elsewhere. A diagnosis of chronic gastric ulcer associated with much inflammatory thickening and matting, was therefore made and a gastro-enterostomy performed. The patient died later of an intercurrent pneumonia and on post-mortem an ulcerating fungating mass was found, which on microscopic examination was found to be a typical adeno-carcinoma. No metastases were seen anywhere.

This/

This teaches one that all tumour growths in the pyloric region, though they may be rarely inflammatory matting, should always be treated as malignant conditions.

We may now pass on to consider some of the signs and symptoms found in the present case.

In the first place, the Pain. This is no doubt due to the erosion by tumour cells of the nerve-endings in the stomach wall. The pain itself is not felt in the viscus since the viscera are themselves quite insensitive to touch or pain, and Mackenzie has shown that pain resulting from a lesion of a viscus is felt not in that viscus, but is referred to the peripheral distribution of the spinal nerve arising from those segments of the spinal cord with which that viscus is connected through its sympathetic supply. In the case of the stomach the sympathetic supply arises from the 5-8th dorsal segment and the pain is therefore referred to the peripheral terminations of the 5-8th dorsal nerves, a distribution which corresponds to the area between the xiphoid cartilage and the umbilicus. This explains the epigastric pain complained of by the patient. But the pain, it will be remembered, used also occasionally to shoot round into the back. The explanation of this is that pain may also be referred to the posterior or lateral branches of the spinal nerves as well as, or even instead of, their anterior branches, and this in the present/

present case the pain was felt in the back (posterior branches 5-8th dorsal nerves) in addition to the epigastrium.

Further in the examination of the patient, it was noted that a small area of superficial tenderness was felt between the xiphoid and umbilicus in front. The explanation of this is as follows:- In the normal state, impulses are constantly passing both in an afferent direction from the viscera to the spinal cord and efferently from the cord to the skin and muscles of the abdominal wall without our ever being aware of their existence. If a viscus becomes diseased the afferent impulses will naturally be of a more irritating nature and the segment or segments of the cord receiving these impulses will be in a state of hyper-excitability. If a cutaneous nerve connected with one of these hyper-excitabile segments receives a stimulus - such as a light pinch which normally would have been quite insufficient to evoke any sensation of pain and which applied elsewhere would fail to do so - it is very probable that pain will be felt; that is the area of skin pinched is said to be hyperalgesic. Theoretically the whole cutaneous distribution of the hyper-excitabile segment might be expected to be hyperalgesic but in practice it is found that certain areas are especially susceptible. These have been worked out and that corresponding to the stomach is found to have its maximal intensity at a point mid-way between the xiphoid cartilage and the umbilicus, which is, as we have seen, the site of the hyperalgesia in the present case.

The explanation of the absence of free HCl has given rise to some discussion.

- (1) B. Moore maintains that it is due to a diminution of hydrogen ions in the blood, as the result of depressed metabolism associated with a cachetic state.
- (2) Langdon Brown suggests that it is due to the loss of gastric Secretin, which is a powerful stimulant to the secretion of HCl. The pyloric region is the one most frequently affected by cancer and though HCl is not formed there, destruction of the pyloric glands involves the loss of the hormonal factor in gastric secretion.
- (3) The fact that the daily total excretion of chlorides in the urine in the present case is not much diminished, would seem to point to the neutralisation of the HCl formed, by alkaline fluid secreted by the surface of a new growth. Reisser has found this in many of his cases.

The symptoms of vomiting and regurgitation are mainly mechanical in origin due to obstruction of the pyloric orifice, but it is possible that here also the absence of HCl may play a part. For Hurst has shown that free HCl in the stomach tends to open the pyloric sphincter and to keep that at the/

the cardia closed. If HCl is deficient, the tendency would be reversed, and thus after food the obstruction at the pylorus would be increased (from absence of HCl stimulating the pyloric sphincter to open) and vomiting thus induced, while the relaxation of the cardiac sphincter (for the same reason) would facilitate both vomiting and regurgitation.

The melaena is due to the continuous ooze of blood from the ulcerated tumour surface, while the constipation is probably owing to the small quantity of food residue which reaches the colon.

Conclusion.

The present case teaches us that amongst the many obtruse factors which enter into the causation of gastric cancer, one definite one is that of chronic gastric ulcer, and that work in the direction of the prevention and cure of this condition will lower the incidence of the disease.

2 CASES OF DIABETES MELLITUS.

Cases IV & V.

A. J. Wilson.

2 CASES OF DIABETES MELLITUS.

CASE A.

William L. Aet 63. Farm-worker.

Admitted to Ward 28 on 3.10.20.

under care of Dr Rainy.

Patient's Complaint:- Pain in the toes of the left foot.

Frequent micturition. Extreme thirst. Rapid loss of weight.

Duration. Pain in toes - 10 weeks.

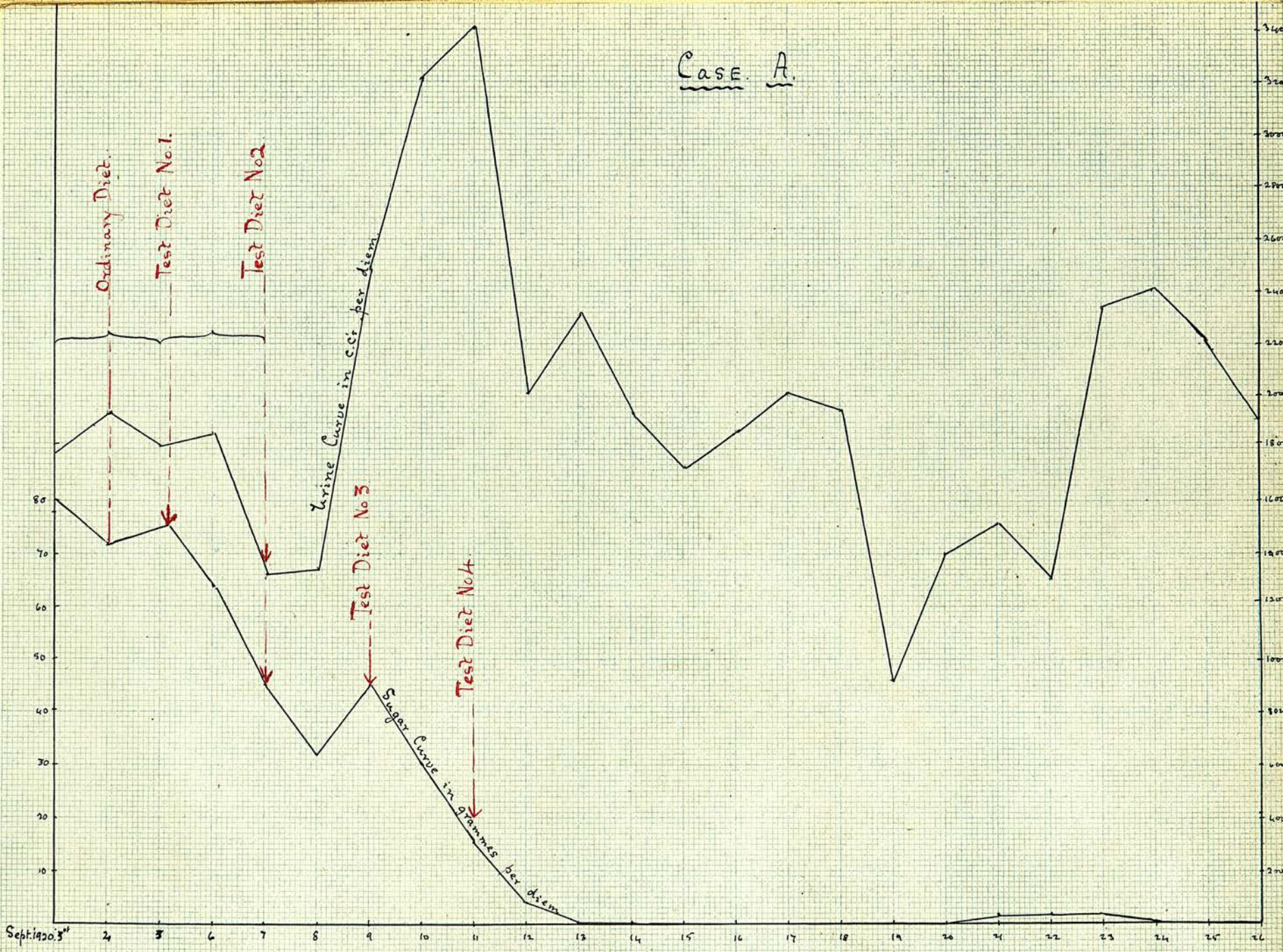
Other symptoms - about 9 months.

History of the Present Illness.

Patient was quite well until about 9 months ago when he began to pass water very frequently and to suffer great thirst. Thereafter he began to lose weight very rapidly.

Ten weeks ago, when he was at work he was suddenly seized with an acute pain in the left calf which finally settled down in the big toe and heel. Next day, the 4th and/

Case A.



Graph to show the effect of diet on the urine and sugar curves.

and 5th toes and later the 2nd became similarly afflicted. The pain is constant, worst at night and when the patient is on his feet. It radiates from time to time across all the toes, on both the plantar and dorsal aspects, and occasionally extends to the heel.

Previous Illnesses.

"Water on the head" (? Hydrocephalus) in infancy.

Otherwise perfectly healthy. No history of specific disease.

No excesses in food or drink previously.

Family History.

No family history of diabetes.

State on Examination.

Patient is considerably wasted and lies still in bed, as movement increases the pain in the toe. The face is slightly flushed. Patient is not of the neurotic type.

Height	5 ft. 4 ins.
Weight	7 st. 13½ lbs.
Temperature	98°

The condition of the toes will be referred to later.

Urinary System.

Micturition is very frequent - every hour, day and night.
No pruritis, or eczema on the genitals or perineum.

Urine:- Pale, with a peculiar pale, bright greenish-yellow tint. Reaction acid. Specific Gravity - 1035.
Cloud of mucous floating on the top. Quantity - 2500 cc.
(approx. 85 ozs.) (For progress of polyuria under treatment, see chart.)

Chemical Composition:-

Sugar (Benedict's method) = 45 grams per diem or 1.8%.

(for progress of glycosuria under treatment see chart).

Fermentation test positive. Phenyl-Glucosazone crystals were obtained.

Albumen - a trace, too small to be estimated by Esbach.

This disappeared when digitalis was given.

Total Nitrogen - 23 grms. per diem.

Ammonia	1 $\frac{1}{2}$	"	"	"
Urea	48	"	"	"
Uric acid	1.15	"	"	"

Phosphates (as phosphatic anhydride) - 3.59 grams per diem.

No blood, bile or pus. No acetone or di-acetic acid.

Centrifuged deposit - a few uric acid crystals, and some hyaline casts.

Alimentary System.

Thirst is intense. Appetite is increased and there is a marked tendency to constipation. Digestion good.

On examination - the mouth and lips are dry. Breath has no odour of acetone. Teeth carious and many are absent. Gums swollen and spongy. Tongue, red, dry and glazed. Nothing to note in the abdomen.

Circulatory System.

No subjective phenomena.

Pulse:- artery extremely tortuous and much thickened.

Frequency 82. Irregular both in time and force.

Pressure (a) systolic 175 mm. Hg. (b) Diastolic 95 mm. Hg.

Heart:-

- (1) Inspection. Apex-beat visible. Extra-cardiac pulsations only in neck (venous - slight).
- (2) Palpation - no thrills.
- (3) Percussion.

$$\frac{III}{2\frac{1}{2}/4}$$

Apex beat in 5th left space 5" from mid-sternal line.

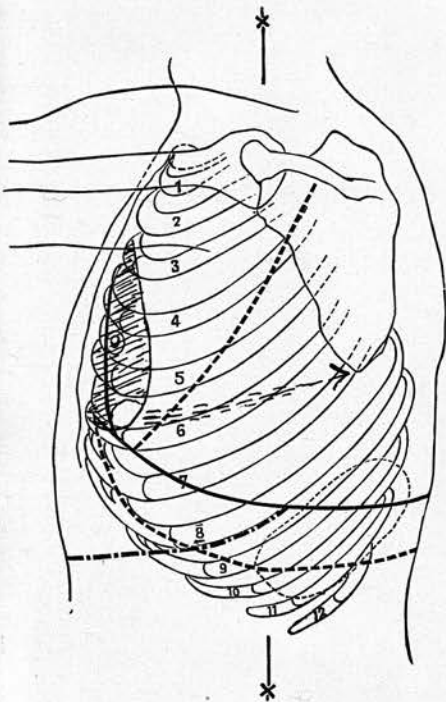
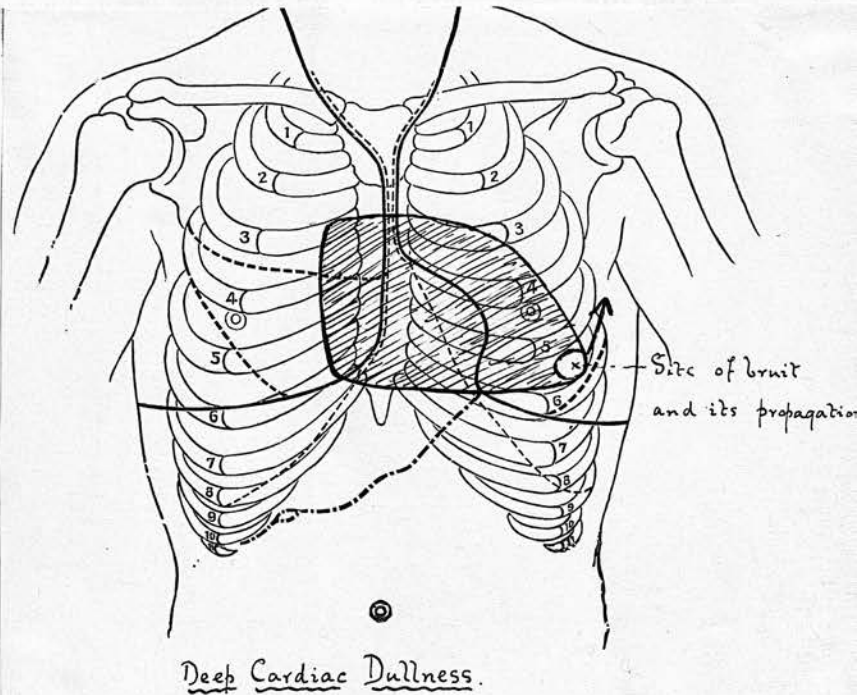


Diagram to illustrate propagation of the Bruit.



Deep Cardiac Dullness.

- (4) Auscultation - rhythm very irregular owing to frequent occurrence of extra-systoles. In mitral area, soft blowing murmur systolic in time, replacing the first sound and conducted into the axilla towards the angle of the scapula. 2nd sound closed in all areas.

Integumentary System.

Skin dry and harsh. No pruritis, carbuncles or boils. Little subcutaneous fat present.

Nervous System.

Muscular power weak, and muscles are atonic. Knee-jerks absent in both legs. All reflexes present elsewhere. No Babinski. No sensory disturbance to be made out, but on the left leg there was some loss of discrimination between blunt and sharp points. On ophthalmoscopy - nothing abnormal found in the fundus.

It may be noted, en passant, that "loss of knee-jerks and most of the sensory disturbances in diabetes are to be associated with vascular changes, rather than with true peripheral neuritis, which is a rare complication". (Osler).

Locomotary System.

The muscles are somewhat hypotonic and wasted.

On admission there was a deep purple color with loss of sensation over the 3rd, 4th and 5th toes of the left foot. (Gangrene). There was good circulation in the popliteal artery, though not in those below.

Progress Notes:-

The progress of the glycosuria under treatment is sufficiently indicated on the chart.

The gangrene remained dry throughout, under the influence of picric acid dressings. Mr Stuart examined the toes on 21.9.20. and decided to operate when the patient's general condition was improved. On 2.10.20 when the urine had been sugar-free for some 10 days, and when the weight had increased from 7 stone $13\frac{1}{2}$ lbs on admission to 8 stone $4\frac{3}{4}$ lbs., patient was transferred for surgical treatment to Ward 16. There, however, a well-defined line of demarcation between the gangrenous toes and the remainder of the foot developed, and the gangrenous parts gradually separated away, thus rendering an operation unnecessary. Consequently, patient was discharged on 4.10.20.

Diagnosis. Diabetes Mellitus.

Prognosis and Treatment. These will be discussed with
Case B.

CASE B.

Thomas M. Aet 42. Restaurant Cook.

Admitted on 14.1.20 to Ward 32.

under care of Prof. Sir Robert Phillip.

Patient's Complaint.-

Great thirst. Frequent micturition.

Marked constipation. Rapid loss of weight.

Duration. 10 weeks.

History of the present Illness.

Ten weeks ago patient began to experience great thirst and to require to pass water frequently. At the same time he became very costive. He lost weight rapidly - in Oct. 1919 he weighed 11 stone 4 lbs., while on admission (14.1.20.) he was only 8 stone 9½ lbs.

Previous Illnesses.

Scarlatina and measles in childhood. Otherwise perfectly healthy. No trauma or mental strain prior to onset of this illness.

Family History.

No history of diabetes in the family.

Surroundings and habits.

Patient is a cook and has worked in a hot and badly ventilated atmosphere for 10 years. He takes very little exercise and was an excessive eater, especially of starchy foods, e.g. cake, bread, potatoes, etc. He also drank a good deal of sweet beers.

State on Examination.

Patient shows very marked wasting. He appears to have been at one time a muscular, well-developed, though obese man. His colour is good. Height 5 ft. 7½ ins. Weight 8 st. 9½ lbs.

Urinary System.

Micturition is very frequent - 8 times by day and 6 by night. No incontinence. No pruritis, or eczema of the genitals.

Urine:-/

CASE B.

(Note: As the daily quantity of urine did not vary to any very large extent, the sugar excretion per diem is represented in grains per ounce. The curve thus gives a sufficiently accurate representation of the progress of the Glycosuria.)

Sugar Curve in grains per ounce of urine.

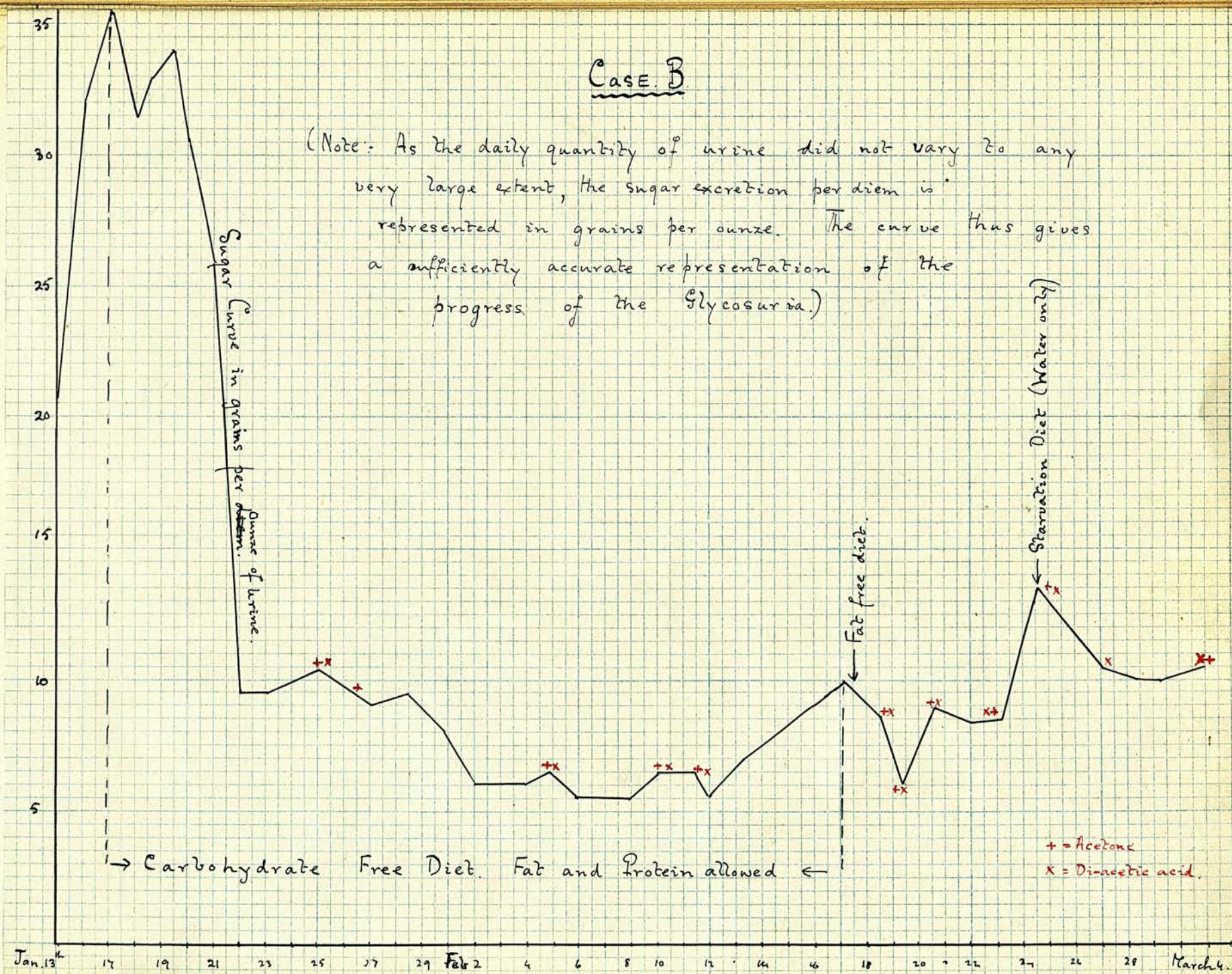
Fat free diet.

Starvation Diet (Water only)

+ = Acetone
x = Di-acetic acid.

→ Carbohydrate Free Diet. Fat and Protein allowed ←

Jan. 13 17 19 21 23 25 27 29 Feb 2 4 6 8 10 12 14 16 18 20 22 24 26 28 March 4.



Urine:-

Quantity averages 300 oz. per day.

Pale and watery in colour with an odour like new-mown hay.
No deposit. Reaction acid. Specific Gravity 1038.

Chemical Composition. (20.2.20)

Sugar estimation (Benedict) averages 36.6 grs. per oz.

(8.36%) (713.7 grams per diem.)

(see chart)

Total Nitrogen - 28 grams per diem.

Ammonia - $2\frac{1}{2}$ grams per diem - this is a very considerable
increase over the normal $1\frac{1}{2}$ and its significance
will be referred to later.

Urea - 51.8 grams per diem.

Uric acid - 1.2 " "

Phosphates (as phosphatic anhydride) 4.2 grams per diem.

Sugar-fermentation test, positive. Phenyl-Glucosazone
crystals obtained.

Blood, albumen, bile, all absent.

Acetone and di-acetic acid both present.

Alimentary System.

Appetite is greatly increased and thirst is extreme.

Prior/

Prior to admission patient drank 1 glass of aerated or other water every 5 minutes. Digestion is good but there is marked constipation.

The teeth are artificial. Mouth and lips dry. Tongue dry and red.

Nothing further to note.

Circulatory System.

No subjective phenomena. Heart not enlarged, and sounds all closed. Pulse - regular: wall only slightly thickened. Blood pressure (a) systolic 140 mm. Hg. (b) Diastolic 85 mm. Hg.

Remaining systems.

Nothing abnormal found.

Progress Notes.

For progress of glycosuria and ketonuria under treatment see chart. On admission - sugar excretion was 21.24 grs. per oz. Under treatment it was reduced to 6.1 but on discharge on 16.4.20 it had again risen to 10 grs. per oz. Diacetic acid and acetone were present throughout the greater part of treatment and persisted up to day of discharge. *

The Prognosis in the Two Cases.

Many factors have to be taken into account in considering this.

(1) Age.

The younger the patient the worse the outlook. In subjects over 40 the course of the disease is usually much more prolonged, a duration of 10-15 years being common. This factor of age is thus ^Yfaçourable for both the patients.

(2) The urine. The continued passage of very large quantities of urine is usually a sign of grave disease. Very large amounts of sugar are also bad, though it cannot be said that the severity of the case is directly proportional to the sugar output. In this respect prognosis in case B, with the daily urinary excretion of 300 oz. and diurnal glycosuria of 713.7 grams per diem as compared with 85 ozs. and 45 grams respectively in Case A, is much more serious.

The most important consideration in connection with the urinary sugar is the effect of the restricted diet in reducing the quantity of sugar excreted. A glance at the sugar curves under treatment in the two cases is again of bad omen in Case B, where even under severe dieting for nearly 3 months, sugar at a minimum of 195 grams per diem continued to be excreted.

The presence of acetone bodies immediately gives a grave character to a case as it then belongs to the class of severe diabetes and is likely to terminate sooner or later in coma. The graph for case B shows that the Ketonuria persisted up to the day of discharge and this is of very grave significance.

Coming now to special points in the prognosis of Case A:-

- (1) "The loss of knee-jerks is common in diabetes and seems to be of no special importance as an indication of the severity of the disease." (Hutchison).
- (2) Gangrene. Gangrene in diabetes is an indication of arterial disease, with consequent deficiency of the blood supply to the affected part. It is of little import, beyond indicating arterial disease.
- (3) The Albuminuria.

"Albuminuria occurring in the course of diabetes, in the majority of cases, is an expression of an insidious nephritis of the interstitial variety, and the patients, for the most part past middle life, show cardio-vascular changes.

The question of prognosis is a mixed one; for when interstitial/

interstitial nephritis develops in the course of diabetes, amelioration may take place in the diabetic symptoms and the glycosuria may disappear. The prognosis then becomes that of chronic interstitial nephritis complicated with hyperglycaemia; that is to say, it is always grave.

Albuminuria due to circulatory disturbance is common in cases of cardiac disease with loss of compensation. In these cases, imperfect circulation leads to deficient oxidation and secondary changes in the renal epithelium. The quantity of albumen present and the examination of the centrifuged deposit will exclude nephritis. Prognosis will depend upon the influence of the therapeutic measures in improving the circulation; with improved general circulation, Kidney function is re-established and a diuresis follows with disappearance of the albumen." (Prof. Boyd, Index of Prognosis).

It is rather difficult in Case A to decide to which of these two groups the albuminuria belongs. In favour of chronic interstitial nephritis is the high blood pressure, the cardiac hypertrophy, the marked arterio-sclerosis and the presence of casts in the urine. While the small quantity of albumen, the existence of a mitral incompetence, and/

and the disappearance of the albuminuria under treatment by digitalis suggests that the albuminuria is congestive in origin, being associated with a temporary failure of cardiac compensation.

- (4) The arterio-sclerosis. "We do not estimate the chances of our diabetic patient in terms of his arteries, but in terms of his output of sugar and the degree to which this can be controlled. Also the progress of arterial change in such persons is relatively slow and the outlook is therefore better than in some types of arterial degeneration." (Rolleston).

The prognosis is thus considerably more favourable in Case A than in Case B. The latter will probably soon succumb to Ketosis and coma, while the former may live for years either quietly dying from gradual cardiac failure of arterio-sclerotic type, or suddenly from a cerebral haemorrhage.

COMMENTARY.

These two cases constitute very complete and typical text-book pictures of Diabetes Mellitus, without, unfortunately filling up any of the blanks in the knowledge of the pathology and etiology of the disease.

The/

The theories which have been brought forward in connection with the disease are legion, but sufficient evidence has now been gathered to indicate that the pathology is intimately associated with changes in the organs which constitute the Endocrinous system, and in particular with changes in the pancreas.

The association of the pancreas with the disturbance of sugar metabolism has now been established by experimental extirpation, originally by Von Mening and Minkowski and lately by Allen. The fact is now demonstrated that the pancreas furnishes, in addition to its external secretion, an internal secretion to the blood and lymph which is necessary for normal sugar metabolism, and it is now generally believed, that in all probability this secretion is derived from the islets of Langerhans. The pancreas is thus a double gland with its external secretion into the intestine and internal secretion into the portal vein.

Microscopically, Allen has found in nearly 85% of the cases he examined, evidence of changes in the islets of Langerhans. This establishes the hypothesis that the islets are intimately related to diabetes, - that in fact their healthy functional activity is essential for the prevention of the disease, - but the exact cause of the damage to the islets remains obscure.

Opie states that in at least 70% of cases, chronic inter-acinar pancreatitis is present with atrophy of the islets. Syphilitic change is said to be a possible factor in some cases. It is thought that certain general diseases may exert a selective pathological influence on the islets, without causing at the time any symptoms of pancreatic disturbance, in a way analogous to the occurrence of orchitis as a complication of mumps. Others again think that a specific toxin or chemical poison may account for some cases, a specificity analogous to that of the tetanus toxin for the motor neurons of the spinal cord. Carcinoma, lipomatosis, interstitial pancreatitis may be factors in a very few cases, but they cause only a temporary glycosuria and even then, only when very advanced. In 10-15% of cases, no pathological changes have been found. Allen, who is one of the most convinced adherents of the pancreatic origin of diabetes, admits that a man may actually die of diabetes and yet have as good a pancreas as normal - ^{so} ~~as~~ that a functional incapacity of the pancreatic cell-islets, due to some nervous influence, must be responsible in these cases and this is the basis upon which Langdon Brown has postulated his Polyglandular Hypothesis (Croonian Lectures 1918).

Brown points out that carbohydrate metabolism is not controlled solely by the pancreas (though it probably takes the/

the leading share) but that all the other endocrinous glands are co-associated. These glands, he shows, fall into two antagonistic groups. The first consist of the pancreas, whose internal secretion promotes the utilization of sugar by the tissues and increases carbohydrate tolerance and is thus anabolic; the second comprises the thyroid, pituitary and the supra-renals, the secretion of each of which mobilises the sugar into the blood and diminishes carbohydrate tolerance, and is thus Katabolic.

The second group have two other features in common besides this effect on carbohydrate metabolism - they are all associated with the activity of the reproductive organs and they all have their secretion controlled by the sympathetic. On the other hand, the pancreas which is anabolic, is, like other anabolic activities, under the control of the para-sympathetic (vagus), and as the vagus and the sympathetic are opposite in effect when applied to the same structure, we should expect that the sympathetic would be inhibitory to the pancreas as it is to other digestive processes. Thus sympathetic irritation would diminish the activity of the gland (pancreas) which promotes sugar utilization and at the same time increases the activity of the group of glands which throw sugar into the blood. It is clear then that anything which diminishes the secretion of the pancreas or increases the/

the secretion of its antagonists will increase metabolism, lower sugar tolerance and may excite frank glycosuria.

Now, when any of the glands controlling carbohydrate metabolism becomes the seat of organic disease, there will be other signs besides the effect on carbohydrate metabolism. Now improved diagnostic methods of recognising signs of disease in these glands has not led to their being found in an increasing number of cases of clinical diabetes. Brown therefore maintains that the only way in which the loss of balance between the internal secretions can be produced is through a disturbed innervation and it is in the sympathetic that we find the one nervous control common to them all.

The disturbance of the sympathetic nervous system is of the nature - according to Brown - of emotional stresses and strains - "when stocks go down in New York" says Crile, "diabetes goes up". The frequency of diabetes in the Jews, the most emotional race, and its association with families of a neuropathic tendency point in the same direction.

The modus operandi of the sympathetic in producing diabetes lies in its function as the part of the nervous mechanism concerned with body defence. Sympathetic stimulation, is, in the primitive state, a preliminary to fight or flight, - "emotion moves us, hence the name" says Sherrington. But under conditions of civilisation the response to emotion tends /

tends to be repressed, while preparations for that response still occur. Among these preparations is the mobilization of blood sugar which is required for the anticipated display of energy, since active muscle consumes $3\frac{1}{2}$ times as much sugar as resting muscle; but the natural response is repressed and does not occur and hence the increased blood sugar becomes habitual and diabetes results.

In the present two cases it is quite impossible to determine the exact etiological factor present - there has been no emotional stress or strain prior to the onset of the illness and which might indicate a type belonging to Langdon Brown's functional sympathetic diabetes, nor is there any indication of organic disease in any of the endocrine organs. One can only assume that there is possibly some structural alteration, with resulting interference of function, in the islets of Langerhans, but the exact etiology and nature of this change is purely problematical.

There are however certain predisposing factors in the causation of diabetes which possibly have played their part in one of the present patients (Case B). One of these is overeating, especially of sugary and starchy foods.

"No other condition rivals in importance obesity from overeating as a fore-runner of diabetes" writes Joslin. Another factor is/

is lack of exercise, - partly by producing the condition of obesity and overweight, but also by disuse of the muscles, for it is largely in these that the sugar formed from the food is consumed.

Before attempting to review the actual changes in the metabolism in diabetes, it might be well to note briefly the normal carbohydrate metabolism. In health the carbohydrates ingested in the food are converted into monosaccharides by ferments in the intestinal juice or mucous membrane and are then absorbed and pass to the liver. In the latter they are transformed into glycogen; sufficient (for tissue use) to maintain the blood sugar at constant level (0.05 to 0.012%) is reconverted at once into dextrose (which is the sole carbohydrate leaving the liver), while the excess is stored as glycogen in the liver at a maximum of about 150 grams. The blood acts purely as a means of transport and communication, and the kidneys act as safety valves. In a given person the amount of blood sugar remains constant, even with muscular exertion, unless extreme. When blood sugar rises too high (above .15% - Graham's "leak-point") - a condition of hyperglycaemia - a glycosuria results. When the dextrose reaches the muscles a certain amount is utilised for the production of/

of energy - which is the essential fate of carbohydrate -, while temporary excess is stored as glycogen at a maximum of 150 grams. As blood sugar falls from muscular exertion, the liver, as a result of a call (by an unknown mechanism) of the need for more sugar, supplies this deficiency:-

- (1) From the glycogen - derived from carbohydrate ingested.
- (2) From proteins of the diet and body tissue - proof of this source is seen from the result of treatment in diabetes, as the glycosuria continues on a carbohydrate free diet and increases with the amount of protein in the diet.
- (3) In health no sugar is derived from fat, as glycosuria is uninfluenced by the amount of fat in the diet. If ingestion of carbohydrate is constantly excessive, the unused balance is converted into and deposited as fat.

Having thus briefly surveyed normal carbohydrate metabolism, one is now in a better position to proceed to the question of that of the diabetic. In this disease, when the monosaccharides arrive at the liver, conversion of part into glycogen takes place as usual, but the liver, though it is able thus to form, is unable to fix and retain glycogen, which is at once reconverted into dextrose and passed into the blood. When the dextrose reaches the muscles, the latter are unable to use it owing to the absence of the pancreatic hormone, (derived/

(derived from the islets of Langerhans), which is essential to enable the muscle to combust and utilise dextrose. A call is therefore sent by the muscles to the liver for more sugar - which the muscles are accustomed to use for the production of energy. The liver responds finally by producing dextrose from the proteins of the diet and the tissues, thus excessively increasing protein metabolism.

This Katabolism results in weakness and wasting so that the excretion of Nitrogen often rises to 20-30 grams daily (23 grams in Case A, 28 grams in Case B.)

Recently important work has been done upon the question whether fat is or is not a source of sugar in diabetes. All are agreed that metabolism of fat in diabetes is abnormal, though at present very obscure, and that in acidosis it is the dominant factor. It has long been believed that fat is not converted into sugar, as administration of fat has little, if any, influence on the amount of sugar excreted but that such conversion does occur, without affecting sugar in the urine or in the blood, is upheld by Graham and Poulton on the following grounds.

- (1) Respiratory Quotient:- When dextrose is completely combusted, the CO_2 output equals the oxygen intake, i.e.

$$\text{respiratory quotient } \frac{\text{CO}_2}{\text{O}_2} = 1.$$

For/

For higher fats the quotient is about 0.7, and lower for proteins. Normally it is 0.9; in diabetes it falls to a figure varying with the severity down to 0.7. This indicates that energy is obtained, not solely from sugar, but also from fats and possibly protein.

- (2) The "D to N Ratio". (viz. ratio of dextrose to Nitrogen excreted in grams). From 100 grams of protein (=16 grams N) 130 grams dextrose is the maximum procurable, based on the carbon present, giving D to N of 8. In severe diabetes on strict diet the ratio is constant at 2.8 or rarely at 3.65; but a few cases are recorded with a ratio of 8, and are not unreasonably claimed by Graham and Poulton as proof of production of dextrose from fat.

In any case, the liver responds to the call from the muscles for more sugar by abnormal and excessive metabolism of protein and probably fat, and the result is, that as the muscles continue to be unable to utilise the additional sugar formed, a condition of hyperglycaemia results. The degree of hyperglycaemia necessary to produce glycosuria requires to be higher in diabetes than in health, i.e. Graham's "leak-point" is/

is raised. Thus sugar may appear in the urine only when the blood-sugar reaches 0.18% (Graham's "high leak-point". This is usually ascribed to the Kidneys becoming less permeable to sugar than in health.

As already mentioned, to provide the sugar required by the muscles, the liver causes abnormal metabolism of proteins. Protein substances including those of the tissues are consumed in an unaccustomed way to develop the necessary energy and this being partly in the form of sugar, becomes useless because of its carbohydrate nature and is excreted with the rest in the urine. Now in time when this source becomes inadequate to supply the energy demands, the fats are attacked and it is then that the greatest danger in diabetes arises.

Zeller has shown that to lead to the consumption of 2 molecules of fat without Ketosis, it is necessary for one molecule of carbohydrate to be metabolised. In the absence of carbohydrate utilisation, there occurs a peculiar imperfect combustion of fats, which is analogous to that seen in the course of starvation, where for another reason no carbohydrate is supplied for energy production to the tissues. When carbohydrates are not utilised as fuel, protein is easily utilised but apparently it takes so much draught to burn them that not enough is left to consume the fats completely and the products/

products of incomplete combustion accumulate in the system and suffocate the patient as effectually as does the CO of a charcoal stove. The chief of these intermediate products is B-oxybutyric acid which is itself the source of di-acetic acid and acetone. These are the so-called "acetone" bodies and though they are excreted in the urine, they are excreted only in part, and as they act as poisons to the body, toxic phenomena appear which are known as the symptoms of acidosis or acid-intoxication.

As to the origin of the acetone bodies, the view given above, viz. that "acetone bodies are produced when metabolism of fat occurs in absence of sufficient metabolism of carbohydrate", is that of Van Noorden, i.e. the condition is ascribed to "deficient oxidation" of fats. Poulton however thinks that in diabetes, fat is converted into sugar and that acetone bodies are produced during this abnormal metabolism. In either case, it is the fats which are incriminated.

To deal with the acid accumulation the tissues attempt, in slight cases successfully, to neutralise the acids first by the alkalies, (e.g. K. Na) already present, secondly by production of ammonia; instead of conversion into urea, large amounts of ammonia combine with the acids, hence the great rise in the excretion of ammonia. Thus in case B where
Ketonuria/

Ketonuria was so persistent, ammonia excretion was $2\frac{1}{2}$ grams per diem as compared with the normal $1\frac{1}{2}$.

The symptoms resulting from the acid accumulation may be due to (1) Direct toxic action of B-oxybutyric acid or (2) Acid intoxication (Stadelmann). Neither acetone nor di-acetic acid is toxic for healthy animals.

Pavy ascribes the coma, to CO_2 narcosis resulting from the acidity of the blood causing lower carrying power, and hence accumulation of CO_2 in the tissues.

Treatment.

The thing of importance from the point of view of treatment which emerges from the above is, that diabetes is characterised by a wasteful metabolism, - "the essence of true diabetes is a waste of the carbohydrates which hurry through the body, in great part never warehoused as glycogen," (Osler) and the proof of this waste, from loss of power of sugar assimilation, and uneconomical protein and fat metabolism, is to be seen in the appearance of sugar in the urine. This sugar loss means a very serious thing to the organism, as sugar having a calorific value of 4.1 calories per gram, many hundreds of calories may be completely lost in the 24 hours. For instance, in case A. on 6.10.20 when food to the value of 1797 calories was given, the sugar loss was 64 grams/

grams for the day, equivalent to 262.4 calories. That is to say that of the food taken, nearly $\frac{1}{6}$ was completely wasted and lost. In case B. things were even more serious, the average sugar loss per diem working out at 713.7 grams or an equivalent of no less than 2826.17 calories, and this is without allowing for acetone and di-acetic acid.

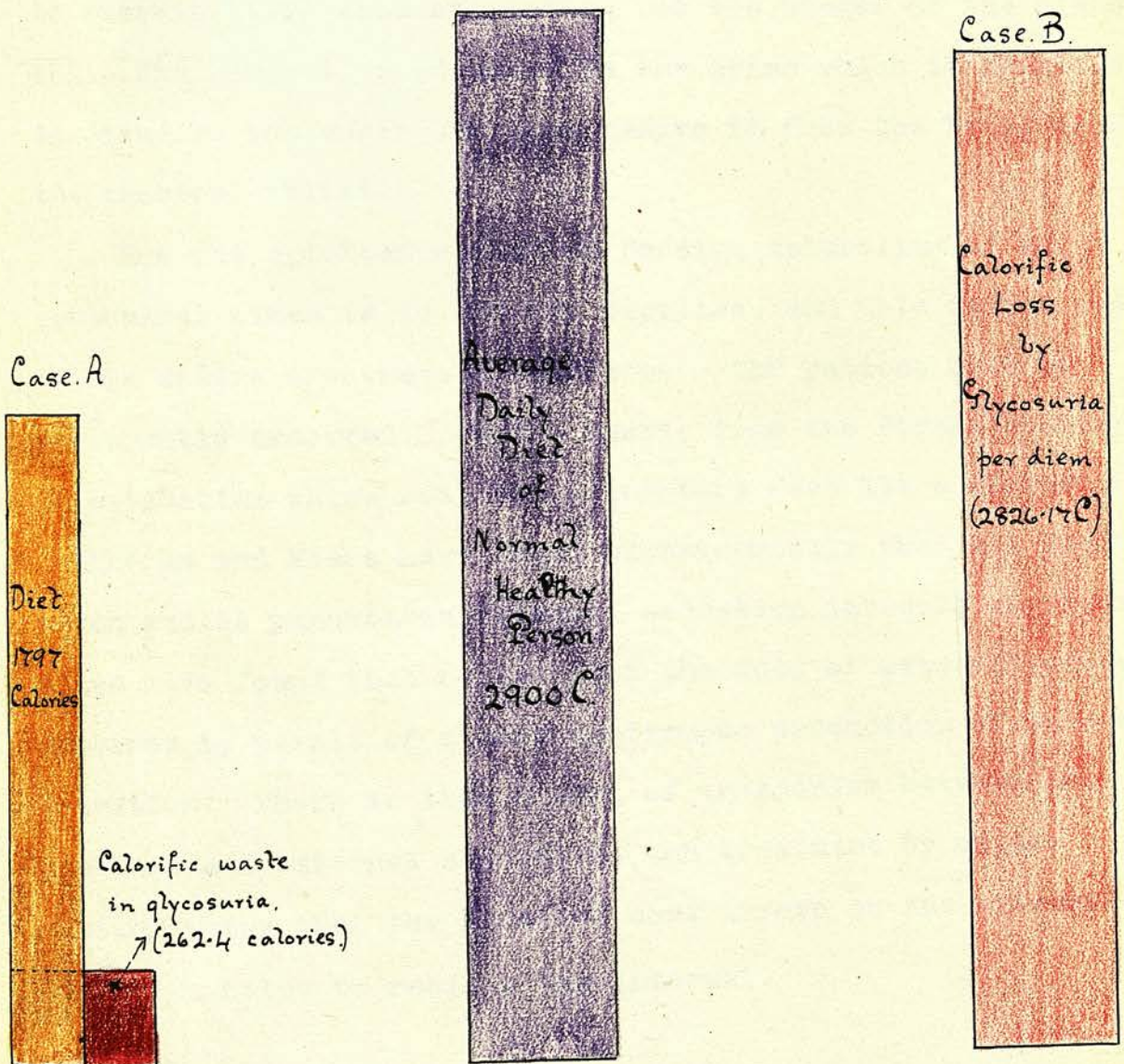


Diagram to illustrate enormous metabolic waste in the daily glycosuria.

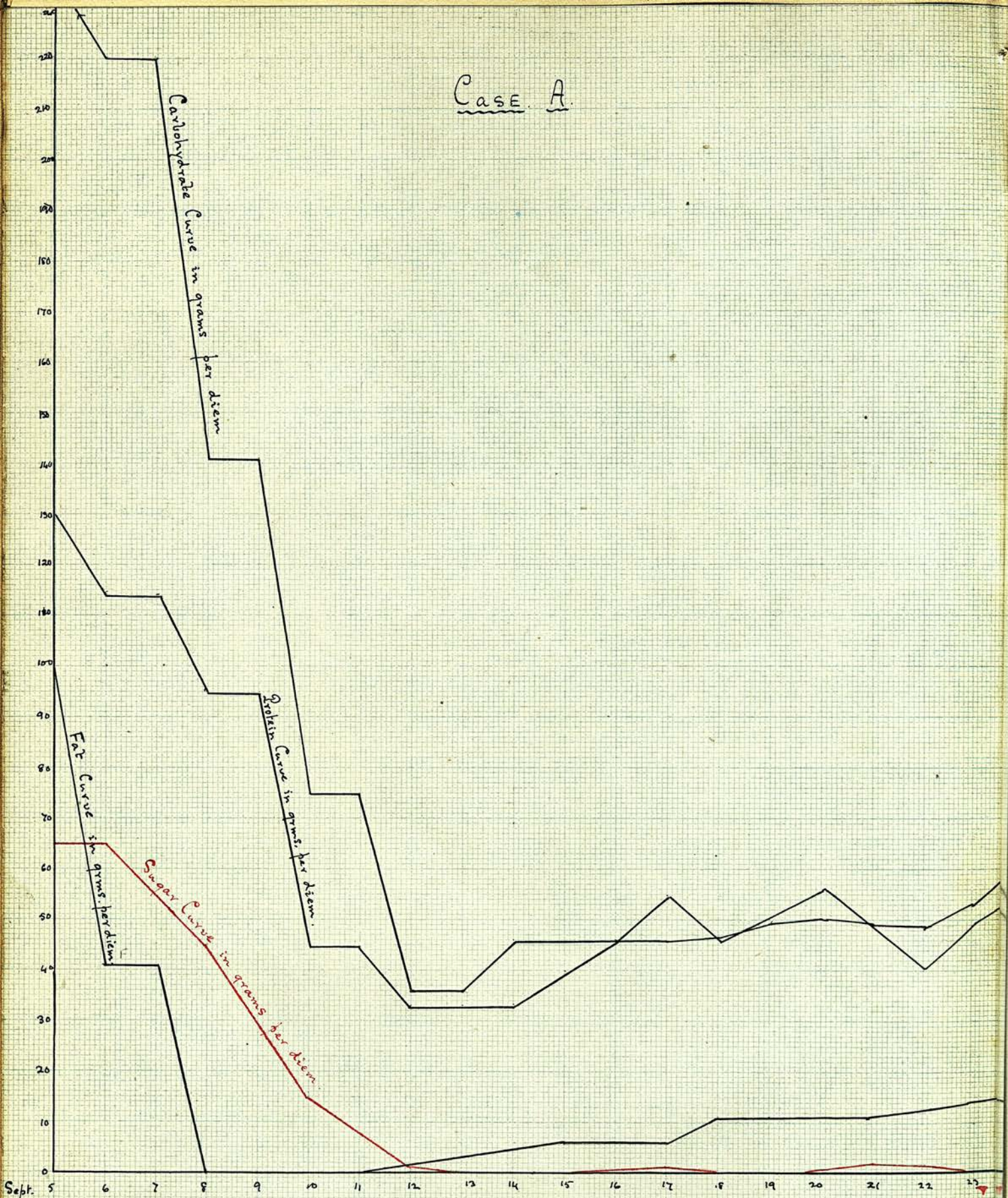
There is further, apart from the actual sugar loss a very considerable daily loss of energy in warming the liquids taken to the temperature of the body, equivalent according to Benedict and Joslin to nearly 6% of the total heat of the day.

As a result of this energy loss more food must be eaten to sustain life, thus accounting for the hunger of the diabetic, while the large loss of water in the urine which is required to dissolve the sugar and thus remove it from the body, explains the abnormal thirst.

Now the quickest method of forcing metabolism to adopt economical lines is to cut off supplies, and this is the essence of the modern treatment of diabetes - the patient must be permanently underfed. Quite apart, from the forced economy in metabolism which results, alimentary rest has a further use. Cohnheims and Klees have found experimentally that all foods which excite pancreatic external secretion increase glycosuria. Allen also found that relief from the duty of external secretion appeared to permit of a more continuous production of internal secretion. There is thus a sort of antagonism between the internal and external secretions, and treatment by under-dieting means that the lessened work thrown on the external secretion helps to restore the internal.

As/

CASE A.



Graph to illustrate effect of dieting on diurnal sugar excretion.

As the great danger in diabetes, i.e. acidosis, is the result of abnormal fat metabolism, the latter was the first of all to be restricted. Subsequently the patient was made sugar free by gradual reduction of carbohydrate and protein, combined with simple fasting. Once the urine was sugar free the second part of the treatment was begun, namely to determine the lowest grade of nutrition at which the patient could live in comfort, without glycosuria or ketonuria.

All the restrictions in diet were made gradually, as any sudden change may evoke acidosis and coma. In case B. Ketonuria continued in varying degree and sodium bicarbonate was therefore given in increasing quantities up to day of discharge.

In case A. when the urine was sugar free for 24 hours, increase in the diet was begun, starting with (a) carbohydrate, small amounts at first, by vegetables of low carbohydrate grade, then through increasing grades and amounts finally to potatoes and bread, the urine in the meantime remaining sugar-free. "Carbohydrate tolerance", i.e. the amount on which sugar commences to appear in the urine, is found, and the carbohydrate diet fixed should not exceed more than two-thirds of this quantity. (b) Protein:- When the urine was sugar free for 2 days, eggs were added, then gradually meat up to 1.5 grams per kilo. of body weight. (c) Fat:- This was the last to be added because of the danger of acidosis. This was given gradually in the form of butter and bacon.

As regards general treatment:- To avoid further loss of energy in chilling of the body - the patients were kept warm. The bowels were kept acting freely by purgatives, as constipation is believed to predispose to the development of coma. Great care was taken in the cleanliness of the skin - any infection through an abrasion might be serious as the excess of sugar in the system renders the body a very favourable culture medium for pus organisms.

Of drugs in the treatment of diabetes - opium preparations, by depressing metabolism, are alone of any use, but there was no indication for their exhibition in the present cases.

Conclusion.

"In spite of the very great advances in treatment and the brilliant success of painstaking investigations into the pathology of the disease (diabetes), it is brought home to one, how little is really known about the condition. Although it is true we prolong the life of the most severe cases for years, during which time the patient feels comparatively well, yet the treatment is, in no sense of the word, really a cure - the most that one can do is to arrest the progress of the disease". (Graham, Goulstonian Lectures, 1921).

A CASE OF TABO-PARALYSIS.

Case VI.

A. J. Wilson.

A CASE OF TABO-PARALYSIS.

James W. Aet 52. Colliery electrician.

Admitted 15th December 1919 to Ward 32 under care of
Prof. Sir Robert Phillip.

Patient's Complaint. Giddiness, "Rheumatics" in the legs.

History of the present illness.

Patient began to be troubled with his "rheumatics" about 6 months ago, and they have never left him since. A week ago on arising from bed he experienced a sensation of giddiness, his head felt swimming but he did not fall. He had never previously experienced anything of this nature. The giddiness continued, except when he lay down, and so he came to the R.I.E. where he was admitted on 15.12.19.

Previous Illnesses.

At the age of 19 when he was in the army, he developed a rash all over the body but denies any sore on the genitals prior to this. No other illnesses apart from this.

Family/

Family History.

Three children, eldest aged 15, youngest 5, alive and healthy. No children dead. His wife has never to her knowledge had any miscarriages, and the children show no evidence of congenital syphilis.

State on Examination.

Patient has a somewhat sallow complexion, with little subcutaneous fat, and a somewhat expressionless - though sad looking - face, with slightly drooping eyelids. He looks generally unhealthy. He suffers from deafness in the left ear.

Weight 9 stone 6 lbs.

Height 5 ft. 6 ins.

Temperature 97.2°.

NERVOUS SYSTEM.Higher Cerebral and Mental Functions.

Patient is of quite average intelligence but is mentally of a very restless and excitable nature - it is somewhat difficult to get him to maintain his attention on the topic being discussed. He seems easily distracted. His conversation is quite rational and even clever but lacks sequence. His wife states that he has been rather "changed" of late, - rather moody, at/

at times depressed and at other times almost boisterous. He has become more "ambitious" and thinks of seeking another situation as his merits are not being sufficiently appreciated.

His memory for both recent and old events is good. Articulation and phonation as tested by test ^{ph}ases is quite unimpaired. He talks rapidly and flits quickly from one to another and often very divergent topic, but there is a definite hesitation between sentences, and when he stops ~~then~~ there is slight twitching of the lips.

There have never been delusions or hallucinations of any kind.

Cranial Nerves.

(1) Olfactory Nerve - no disturbance of smell.

(2) Optic Nerve.

Subjective phenomena:- Patient has been suffering from a gradual failure of vision, first in the left eye and then in the right, and this has become progressively worse, so that he cannot distinguish objects if at any distance. Patient says that on two occasions in the past he saw double - this was transient and soon passed off.

Aonity/

Acuity of Vision (as determined by Snellen's types)

Right Eye $\frac{6}{12}$

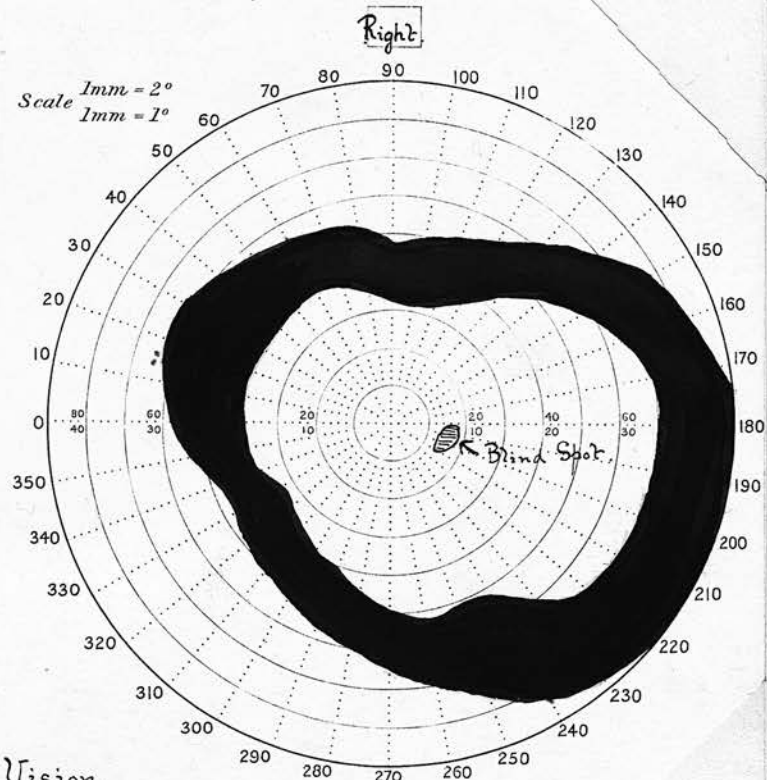
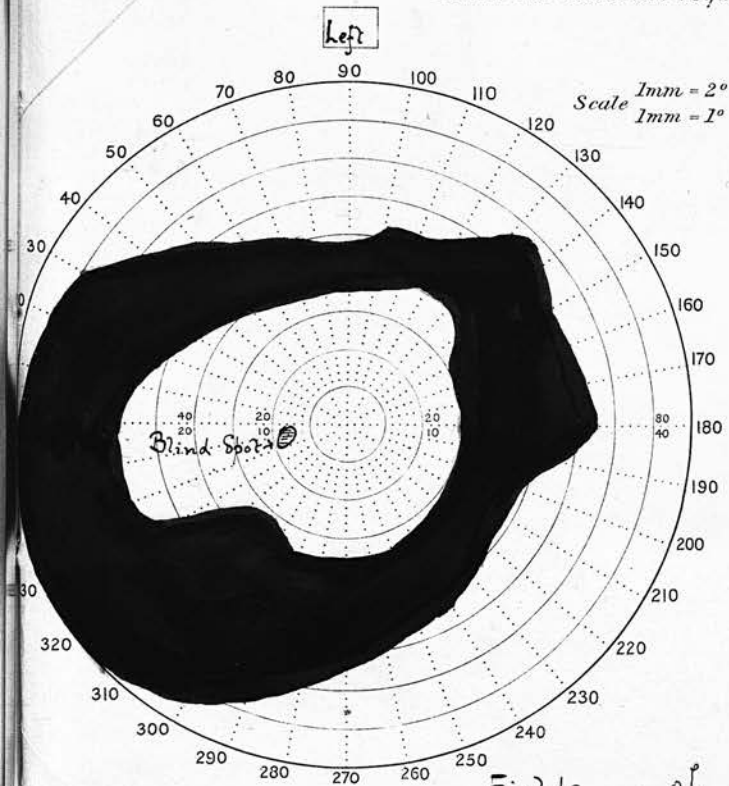
Left " $\frac{6}{18}$

Fields of Vision (see chart)

Right eye - slight concentric diminution.

Left " - field much limited especially on the temporal and nasal sides; to a less extent in other directions.

Stroke out Scale not required. Mark out blind spot.



{ Black = Normal Field
White = Patient's "

Ophthalmoscopic Examination:- Disc pale and somewhat mottled, arteries small and edges rather sharp, these changes being more marked in the left eye. These phenomena indicate a primary optic atrophy.

(3) Oculo-Motor, Trochlear and Abducent Nerves:- Free movement of both eyes in all directions. No squint or nystagmus. Slight ptosis of both eyelids giving the face a dull expression but there is no real paresis of the levatores.

The Pupils:- Both pupils are extremely small (myosis) and are unequal in size, the right having a diameter of about 5 m.m., and the left only about 3 m.m. The left is irregular in outline. Both fail to respond to light, and the right (but not the left) reacts on convergence - Argyle Robertson phenomenon. In both, the cilio-spinal reflex is absent - (this is important in diagnosis and will be referred to later.)

(4) Acoustic Nerve.

(a) Auditory portion. Patient has been deaf in the left ear for the past 2 years. There has been no discharge from the ear.

Otoscopy showed a normal membrane.

Rinne's Test positive.

Weber's/

Weber's Test - tuning-fork heard better on sound side.

Schwabach's Test - bone-conduction markedly diminished.

The deafness is therefore in the sound perceiving apparatus - nerve-deafness.

(b) Vestibular part.

The giddiness of which the patient complains is true vertigo, i.e. external objects seem to move round him. Examination of the vestibular apparatus to determine the nature of this vertigo could not be made owing to lack of a rotation chair.

(5) Remaining cerebral nerves - nothing abnormal found.

Motor Functions.

Slight tremor in outstretched hands. Motor power is undiminished. The gait is unaltered - patient walks quite steady and straight and there is no swaying from side to side. He has no difficulty in turning. It has already been noted that he experiences difficulty in walking at night in the dark.

There is evidence of some inco-ordination in fine movements as when patient is asked to pick up a pin the hand hovers over it and fumbles before it can be lifted.

Romberg's/

Romberg's test was negative, but if in addition to closing the eyes and approximating the feet, the body was bent forwards, swaying movements occur.

Reflexes.

(1) Superficial.

Conjunctival)
Abdominal) present.

Pharyngeal reflex:- there is no retching when the finger is thrust between the fauces.

Cremasteric - present.

Plantar - flexor response.

(2) Deep.

	Right Leg.	Left Leg.
Knee-jerks	absent	sluggish
Ankle-clonus	present	present
Ankle-jerk	absent	present.

(3) Organic reflexes are present, though micturition is slow and hesitating and there is marked tendency to constipation.

Sensory Functions.

(1) Subjective.

For the past 6 months, patient has suffered from/

from "rheumatics" in both legs, and was treated for "sciatica" by his doctor. These consist of sharp knife-like pains, shooting in character, which come on suddenly, and last only a few seconds. They are not confined to any one particular region of the leg. They may appear first in the thighs, and then suddenly disappear, to reappear a few minutes later in the calf or heel. They come on in bouts, which last usually an hour or two and then go away, and may not return for 4 - 5 days or even a fortnight, the interval depending upon the weather; cold, wet weather and cold winds increase this frequency. After the pains go away, patient's skin is left very sensitive, but this condition gradually wears off.

Three months ago patient experienced a sudden severe twisting pain in the epigastrium, which had no relation to food. It was accompanied by nausea, and a feeling of faintness. Soon vomiting set in, first of food and then of green-stained mucous, with an acid taste. Patient called in his doctor who said it was a "bilious-attack". This condition continued for about 3 hours and then suddenly ceased, after which patient felt quite well though somewhat exhausted.

Patient had a similar attack 6 weeks ago, but has never been troubled with this since admission to hospital.

There/

There is no "girdle" feeling of constriction round the chest and no abnormal sensations in the sole of the feet when walking. There have never been any fits.

(2) Objective Examination.

Tactile sensibility is of average acuteness, but there is loss of accurate localisation and a certain amount of delay in the appreciation of pain. There is no anaesthesia anywhere. Thermal sensibility is undiminished, there is no intolerance to heat or cold. Muscle-sense and appreciation of size, shape, weight, and form is unimpaired. Pressure on the testis causes little ^{pain}, and there is definite analgesia on squeezing the calf-muscles.

Pressure on the trunk of the right ulnar nerve in the ulnar groove shows ulnar-analgesia. This is of importance from the point of view of diagnosis and will be referred to later.

Muscles and Joints.

Muscle power (grip etc.) is well developed, and muscle tonicity is normal. No alteration in the joints.

Circulatory System.

No subjective phenomena.

Pulse:- 72. Rhythm regular in time and force. Wall thickened.

Pressure:-	diastolic	85 m.m. Hg.
	systolic	130 " "

Heart - nothing abnormal made out.

Haemopoietic System.

Red Cells	4,120,000
Haemoglobin	85%
Leucocytes	7,145
Colour Index	.87.

Wassermann Reaction +++ .

Reproductive System.

Sexual appetite has been diminished of late.

Remaining Systems:- nothing abnormal discovered.

DIAGNOSIS AND COMMENTARY.

The clinical findings may thus be summarised:-

- (1) Argyle-Robertson phenomenon and irregular, unequal, miotic pupils, and a history of transient diplopia and gradual and progressive weakening of vision, with evidence of optic atrophy.
- (2) Disturbances of special senses - auditory (deafness), vestibular (vertigo), and of general sensation - analgesia, etc.

(3)/

- (3) "Lightning pains" and gastric crises.
- (4) Wassermann +++ .
- (5) Certain vague but definite changes in the higher nervous functions.

This clinical picture is absolutely diagnostic of one of two conditions, viz. pre-ataxic Tabes Dorsalis or the early initial stage of General Paralysis of the Insane, and it is of the utmost importance - from the point of view of prognosis, even though it matters little from that of treatment - to determine which of these two is the morbid entity in the present patient.

The frequent co-association of these two conditions has long been recognised, and is not to be wondered at when one considers the pathology and etiology of the conditions. The two diseases may merge indistinguishably into one another, for every feature of pre-ataxic tabes may exist in the early stages of general paralysis. Such cases, Osler has classified as Tabo-paralysis, and the symptom complex of which they are made up, consists of a combination of those of the two conditions and so varies greatly.

Some authorities, notably Möebius, Raymond and Mott even go to the length of maintaining that both diseases are two manifestations/

manifestations of the same morbid entity, and that it is only the difference in localisation that determines whether the morbid process gives rise to the clinical picture of Tabes or to that of General Paralysis. "I maintain", says Mott, "that etiologically and pathologically there is one Tabes, which may begin in the brain, especially in certain regions - (giving Encephalic Tabes), or in the spinal cord in certain regions (giving spinal Tabes or Locomotor Ataxia), or in the peripheral nervous structures concerned with vision, or in nervous structures connected with the viscera, constituting, therefore different types, any of which may be present, or be associated with one or all of the others." (Fournier has taken practically the same view; describing them together under the head of "Les Affections Parasyphilitiques").

It has been suggested that stress is the factor which determines the location of the process and that men whose occupations require much bodily exercise would be apt to have tabes, while those whose activities are largely mental would suffer from paresis. This suggestion is interesting in the present case for patient was for many years in army life, before being burdened with the civilian worries of recent years.

The/

The association of specific infection with both these diseases has long been recognised, but they were formerly considered to be due, not to definite syphilitic deposits, but to the indirect effects of the syphilitic poison, or to its after-effects, and were said to be para-syphilitic diseases.

Their syphilitic origin was long ago suspected by Möebius "the longer I reflect upon it, the more firmly I believe that they never originate without Syphilis".

The luetic origin has now been firmly established by the accumulating evidence of preceeding syphilis (89% in Erb's cases) as determined by the Wassermann reactions and the discovery by Noguchi of the spirochaeta pallida in the brain of the general paralytic and in the tabetic cord.

Reference to recent work on the syphilitic etiology may conveniently be made here. Levaditi and Marie maintain that there exists a plurality of strain of the syphilitic virus and that ordinary syphilis is due to a dermatropic treponema, while general paresis and tabes are caused by a neurotropic. Harrison (1921) thinks that this is most unlikely as a neuropathic virus would soon die out from failure of being transmitted to others. Opinion on the matter is still divided.

Not all workers are convinced of the spirochaetal origin of these diseases. Ford Robertson thinks that they are due to the/

the action of a bacterial toxin - especially ^{of} a Klebs-Löffler bacillus - acting upon a prepared soil, the normal defences having been weakened by predisposing causes, such as alcohol and possibly syphilis.

Now comes the question, is the patient suffering from Tabes Dorsalis, or is he the victim of a commencing General Paralysis? The slight, though suspicious and definite psychical changes noted, and above all the evident optic atrophy, together with the below-mentioned consideration, help to settle this question.

"Optic atrophy when it occurs in the pre-ataxic stage of tabes, usually indicates that ataxia will never be pronounced but unfortunately it is frequently followed by the occurrence of mental symptoms. Mott believes that about 50% of his asylum cases of Tabo-paralysis had preceeding optic atrophy". (Osler)

"When optic atrophy develops early and is leading to blindness, ataxia rarely if ever supervenes, but the mental symptoms of Paresis frequently follow". Buzzard.

"Optic nerve atrophy - one of the most serious events in this disease (Tabes), has this one hopeful aspect - that inco-ordination rarely follows and the progress of the spinal symptoms may be arrested. But on the other hand mental symptoms are more/

more likely to follow". (Taylor.)

"Loss of the cilio-spinal dilatation reflex and the presence of the ulnar signs are more frequent in general paralysis and especially in tabetic forms of general paralysis than in any other form of syphilitic disease of the central nervous system." (Erb).

Upon the significance of the optic atrophy and loss of dilatation reflex and the presence of the ulnar signs taken in conjunction with the psychical phenomena noted, a provisional diagnosis of Tabo-paralysis, may justifiably be made.

In the present patient, infection probably took place at the age of 17 - 18, (the rash appearing when he was 19), so that 33 years have elapsed before the present manifestations appeared. The absence of other specific lesions in the patient and of congenital syphilitic manifestations in his children and of miscarriages in his wife is somewhat puzzling, but very recent investigations by Dr Sanguineti (La Riforma Medica, April 1921) throw light on this question.

Syphilologists have never denied the existence of two well-marked forms of syphilis, one developing without cutaneous mucous and grave visceral lesions, the other affecting slowly the nervous system. Now Sanguineti has studied 100 cases of General Paralysis, inquiring specially into the condition of the consort and descendants, and hence the relationship with the/

the two different forms of syphilis which he thus describes; a latent syphilis, which after the primary infecting sore, is free from specific manifestations, and a florid syphilis which gives rise to the well known secondary symptomatology.

In the first case the infection is due to a neurotropic treponema which from the commencement will fix itself in the brain; in the second case it is the generic treponema which is concerned and ordinary syphilis results. Neurotropic syphilis gives rise to a gradual paralysis which may break out 10 - 15 years after infection, and at the onset reveals itself in phenomena of psychic and somatic exaltation, leads to late dementia, leaves intact for a long time the general physical condition, does not infect the consort, gives a negative Wassermann, and induces to an offspring of irregular development, but of marked precocity. The other, ordinary syphilis, causes on the other hand a general progressive paralysis with very different characteristics, in that it begins 2 to 3, or 25 to 30 years after infection, leads to rapid dementia with bodily and psychic depression, infects the consort, gives a positive Wassermann, and induces onwards an offspring late developmentally with signs of hereditary syphilis. Sanguinetti admits, however, the existence of mixed forms in which elements of both one and the other are found, when the soil offered by the patient allows the treponema to fix/

fix itself early in the nervous system after having given rise to well marked specific manifestations, and to such "mixed" group our patient probably belongs.

Prognosis.

Agreement on the antagonism between the ocular symptoms and the progress of the ataxia, is evident from the above references. The prognosis quo ad vitam is worse than if the case were simple tabes, for tabes does not necessarily shorten life - many patients may outlive their physicians, and the prognosis as to the mind is still worse. The patient will, if he is not carried off in the meantime by rapid recurrences of his gastric crises (or the development of other visceral crises) or in the later stages by bed-sores or bladder-trouble or, (what is still more likely by intercurrent diseases), - will probably get worse both in body and mind and die a hopeless and emaciated general paralytic.

Treatment.

Neo-salvarsan was given intravenously - .45 gram.(weekly). Anti-syphilitic treatment appears on the whole to have been unsatisfactory. Ehrlich considers that this is due to the size of the Salvarsan molecule which is too large to allow it to pass through endothelial membranes and thus prevents it/

it coming into contact with the seat of the disease.

If the gastric crises become worse, division of the dorsal roots supplying the lower thoracic and upper abdomen may be carried out, a procedure in which Thorburn (Practitioner, May, 1921) records a successful case.

The principal point that emerges is that all cases of Syphilis should be efficiently treated before the nervous system is attacked.
